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13. ABSTRACT (Maximum 200 Words)

This document describes the research accomplishments of the Department of Defense funded research to develop, implement, and evaluate models of organ motion and setup uncertainty for dose calculation of modulated electron radiotherapy (MERT) treatment of the breast. The premise is that MERT treatments will deliver a more conformal dose to the breast while minimizing the dose to normal tissues over conventional photon techniques. We have completed the following tasks: (1) developed theoretical models of organ motion and setup uncertainty based on published data, (2) implemented those models into a Monte Carlo dose calculation code, (3) validated our Monte Carlo implementation, and (4) evaluated the efficacy of MERT compared to both conventional photon breast treatment and intensity modulated radiotherapy (IMRT) for breast treatment. In the course of this research, we have found that MERT treatments give a lower peak lung and heart dose when compared to conventional treatments and organ motion/setup uncertainty have the effect of reducing hot spots and mean dose in the target while spreading the low dose components over a slightly larger anatomical area. This project and the other related DOD funded research have allowed the development of MERT as new treatment paradigm for breast cancer.

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Introduction

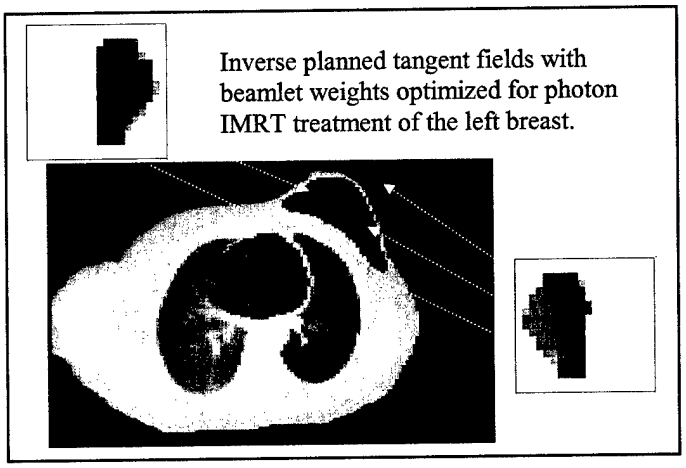
Energy- and intensity-modulated radiotherapy (MERT) is the optimization of many small beamlets of different energies and intensities to produce a highly conformal dose distribution. Each individual beamlet's dose distribution must be calculated in a computed tomography based representation of the patient. The relative weight of each beamlet is optimized using a computer implemented mathematical technique. When the optimized beamlet weights are applied to the patient, a conformal dose distribution is achieved. This is called inverse planning and produces very conformal dose distributions when coupled with MERT. When applied to radiotherapy breast treatment, MERT dose distributions conform to the treated breast while, at the same time, spares the lung, heart, and contralateral breast to excessive irradiation. Two effects that thwart MERT treatments are, inaccurate dose calculation, and the effects of patient organ motion and daily setup uncertainty.

The overall aim of this project is to use accurate Monte Carlo dose calculation as the basis for the development and implementation of mathematical models of both organ motion and setup uncertainty. Monte Carlo is generally accepted by the medical physics community as the most accurate dose calculation model available. Once Monte Carlo is combined with realistic models of organ motion and setup uncertainty, we can include those effects into the calculation of beamlets for optimization. Models of organ motion and setup uncertainty are developed, implemented so we can study the improvement in the MERT dose distributions when these deleterious effects associated with radiotherapy treatment are included in the beamlet calculation and optimization processes. The successful completion of this project facilitates the implementation of MERT as a realistic clinical option for breast cancer treatment. All patient-related factors are included in the dose calculation and optimization processes to obtain clinically realistic dose uniformity in the target volume and normal tissue sparing. As a result of this and other associated research we believe that MERT treatment for breast cancer has a high probability of becoming a clinical reality.

Body

Traditional radiotherapy treatment for breast cancer consists of two tangential photon beams. The tangential beam configuration is used to limit the dose to the lung (and heart for left breast treatment) by limiting the beam divergence into these normal tissues. However, even with this approach, conventional radiotherapy breast treatment is associated with unwanted radiation complications[1-6]. A newer clinically accepted treatment technique is intensity modulated radiotherapy (IMRT). IMRT is a photon treatment that divides the open beam into many small beamlets to deliver a conformal dose to the target. However, this treatment technique is fraught with the same problems as conventional treatments. These problems include: high dose to the heart and lung (resulting in radiation pericarditis and radiation pneumonitis), increased radiation scatter to the untreated breast (resulting in an increased risk of secondary cancer), and poor cosmetic results for patients with larger breasts. A novel approach using electron beams, rather than photon beams, has been proposed to overcome these problems[7-8]. In this technique, a conventional broad electron beam (25x25 cm^2) is subdivided into many small electron beams (1x1 cm^2), called beamlets. Each beamlet can then be subject to energy- and intensity modulation. This is done by initially calculating the dose distribution for each beamlet of different electron beam energies in the patient. Then, a computer implemented optimization algorithm is applied to each beamlet in order to determine the optimal intensity for each beamlet energy. The result is a highly conformal dose distribution to the treated breast with minimal dose to adjacent normal tissues. This approach is called energy- and intensity modulated radiotherapy (MERT) and is a technique called inverse planning. It is the physical characteristics of electron beams that give MERT a real advantage over photon beams in treating breast cancer with radiation. In the past, various theoretical and technical limitations have not allowed the dosimetrically advantageous MERT

Schematic of the conventional method of radiotherapy breast cancer treatment. One of the tangential photon beams is shown.



Inverse planned tangent fields with beamlet weights optimized for photon IMRT treatment of the left breast.

treatments to be used in the clinic. Additional theoretical limitations, which are the subject of this research, are the organ motion and daily setup uncertainty associated with radiotherapy breast cancer treatment. It is worth noting that organ motion and setup uncertainty have a negative effect on all radiotherapy treatments. By including the effects of organ motion and setup uncertainty into accurate Monte Carlo beamlet calculations for the optimization algorithm, we will ensure that beamlets calculated for MERT will be optimized for a clinically real situation and thus, the planned and delivered doses will be the same. The MERT technique will be a very promising modality for breast cancer treatment provided all clinical circumstances are accounted for in the planning/dose calculation process. The successful completion of the project will help the clinical realization of MERT to improve the target dose uniformity and conformity and reduce dose to the lung, heart and contralateral breast.

This project has 4 specific aims: (1) develop models of organ motion and setup uncertainty, (2) implement the models into Monte Carlo dose calculations, (3) verification of the new Monte Carlo code, and (4) evaluate MERT treatment plans of breast cancer cases. We report on the research accomplishments associated with the tasks outlined in the approved "Statement of Work" below for our research between August 1, 2000 and July 31 2003.

1. The Monte Carlo dose calculation code system

We have developed a general purpose Monte Carlo EGS4[9] user code MCDOSE[10] that can be used for patient specific electron dose calculations. Excellent agreement was achieved between the MCDOSE results and measurements and the well benchmarked EGS4/BEAM/DOSXYZ code[11]. Over the course of this research, this code has been significantly enhanced and a new code, MCSIM, has been developed[12]. Our Monte Carlo code system includes the option to produce beamlets for both photon and electron treatment optimization.

2. Computer model of organ motion and setup uncertainty

Tumor motion due to respiration during radiation treatment will lead to "motion artifacts" in dose distributions. Intra-fraction organ motion creates a broadened dose penumbra, which limits the conformal dose coverage to the tumor. From the nominal CT for treatment planning, two more CT slices were generated at inhilation and exhalation. A schematic representation of three CT scans is shown in Figure 1. For the work presented here, the breathing motion is modeled as a periodic wave

with 0.6cm amplitude and 2 sec period. We have also developed analytical models to trace the motion of the tumor in lung based on the initial patient computed tomography data and the motion data measured during a radiotherapy breast treatment. This allows the reconstruction of realistic dose distributions received by the patient during a fraction of treatment. The patient geometry at any time during a breathing cycle is reconstructed using the computed tomography data taken at the inspiration and expiration phases. Accurate correlation between the voxels in the inspiration (or expiration) geometry and the voxels in the reconstructed geometry at any point of the breathing cycle is established so that the dose to a voxel (or an organ) can be accumulated accurately during a treatment[13,14].

The intra-fraction setup uncertainty is a random phenomena[15,16] having a Gaussian distribution. The variance of the Gaussian distribution is different for each translational axis and depends on the anatomical region being treated. We used a "real-time" method to incorporate setup uncertainty into our Monte Carlo calculations. This was done by perturbing the incident particles before they enter the patient. The perturbation was done by sampling from three individual Gaussian distributions, one for each translational x, y or z axis in the patient (i.e., Anterior-Posterior, Right-Left and Superior-Inferior). The variance of the each Gaussian distribution was obtained from the literature[15]. Setup uncetainty was assumed to consist of x, y and z translations that are independent. The model is shown schematically in Figure 2. Our approach to include setup uncertainty is different than a simple Gaussian smoothing after the dose has been calcualated. The "real-time" perturbation of each incident particle before it enters the patient ensure that each particle that enters the patient "sees" the correct source-to-surface distance and heterogeneities within the patient.

3. Implementation and effects of organ motion and setup uncertainty

Our method has been implemented for Monte Carlo treatment planning by interfacing with the MCDOSE code. MCDOSE phantom files for different phases of the breathing cycle were generated and the 3D dose data were obtained from MCDOSE simulations. The final dose distribution was reconstructed from these 3D dose data. The purpose of this work was to compare the effects of organ motion, specifically thoracic movement on conventional photon and modulated electron beam dose distribution. For this part of the work we compared 6MV tangential beams and MERT. The MERT treatment consisted of applying multiple beams consisting of 6, 9, 12, 16, 20 MeV energies to conform the prescription dose of 50 Gy to the target.

There was not a significant change in dose to the target with simulated motion of one cm

posteriorly and anteriorly with respect to the original patient computed tomography scan. MERT showed an improvement in conformity of overall dose to the target as well as avoiding dose to the lung. For photon beam treatment the right lung beneath the target breast shows a disparity in absolute dose and the volume of tissue irradiated at different phases of the breathing cycle. During exhalation, 7% of the right lung volume received a dose of 17.5 Gy while at inhalation, 7% of the right lung volume received a dose of 35.5 Gy. At mid-plane between the two extremes of the cycle only 2% of the right lung received a dose of 35.5 Gy. For MERT, the lung dose remained negligible, however, there was an increase in lung dose during inhalation. Ten percent of the lung received a dose of 5 Gy, which was a dose increase of 5% from the median plane of breathing cycle. The maximum dose to the lung during inspiration was 87% of the prescription dose while at median phase of the breathing cycle the maximum dose decreased to 80% of the prescription dose and at expiration this dose was less than 6% of the prescribed dose when using photon beams.

Similarly, Figure 3a and 3b ahown the effects of organ motion on IMRT breast treatments. Again, 50 Gy was the prescribed to the target. Figure 3a shows the dose and dose-volume histogram for the static CT scan. The real situation is shown in Figure 3b where the effect of organ motion is considered. The dose-volume histograms for these two cases show that when organ motion is included in the calculation, the dose to the target is decreased with a nominal increase in the overall low dose to the lung.

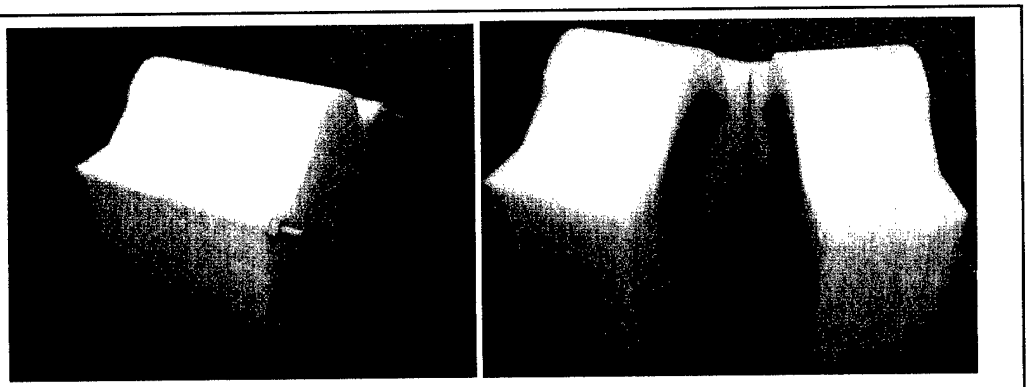
Results obtained using our approach to include setup uncertainty in Monte Carlo IMRT dose calculations was demonstrated for a clinical photon beam inverse planning case. We present a case treated for a lesion in the thorax and planned with 5 inverse planned coplanar fields of 4 MV photons. The setup uncertainty will be the same for other treatments in the thorax like the breast. An interesting aspect is demonstrated in the case shown in Figures 4a and 4b. Figure 4a shows an axial dose distribution for Monte Carlo calculations with and with out setup uncertainty for the second clinical case. In Figure 4b, the target dose-volume histograms for the second clinical case show a slight increase in target dose homogeneity when setup uncertainty is considered in the IMRT dose calculation. We believe the reason for this is that the hot-spots within the target will be smoothed away. It is worth noting that IMRT treatment plans typically have a large dose gradient across the target volume. The gradient can be upwards of 30% in some cases. Setup uncertainty then, will smooth these high dose regions and provide a more homogeneous dose to the target. However, this smoothing will come at the expense of an increased dose to adjacent critical structures. The amount of that dose increase may depend on the shape and location of the target. For critical structures distal to

the target and in low dose regions, the effect of setup uncertainty is not large. Although not shown in this dose-volume histogram, it is also worth noting that the dose-volume histogram to the entire patient's body (skin) are the same for both cases so the total energy deposited in the patient is the same for our simulations with and without setup uncertainty. The dose is simply spread over a large volume to other tissues.

Similar to a simple Gaussian smoothing of the static dose distribution, our method is equivalent to including the effects of setup uncertainty over an infinite number of small fractions[17-19]. Our method of including the setup uncertainty implies that all the statistical fluctuations associated with setup uncertainty have been averaged out to the maximum possible extent. There may be cases with less differences and there may be cases with greater differences in the dose-volume histograms. We feel that by including setup uncertainty in our method at least gives the clinician a reasonable estimate of the possible effects of setup uncertainty during treatment. Additionally, our method does combine proper consideration of a patient's heterogeneities and irregular contours by accurate Monte Carlo dose calculation.

4. Validation of the code

We have validated the code using an independent phantom. The PMMA cylinder is 30 cm in diameter and 40 cm in length. The cylindrical insert has a 4.5 cm outer diameter and 1.5 cm inner diameter, which holds the ionization chamber in the middle. Cylindrical inserts made of PMMA, lung and bone of different densities were available. The cylindrical insert can be moved along the radius and the PMMA cylinder can be rotated around its central axis. The slab inserts are 5 cm wide and 0.1 - 5 cm thick. One of the slab insert can also hold a chamber. The PMMA cylinder is supported at the ends by two 2 cm thick craters which are glued to a 0.5 cm



An anthropomorphic breast phantom. Constructed out of tissue equivalent polystyrene and cork to simulate the low density of lung tissue. The view on the right is the complete phantom and the view on the left shows the lung inside the phantom.

thick PMMA base plate. A picture of the phantom is shown in Figure 5. Note that the ion chamber is also shown in the picture. Figure 6 shows a dose distribution for validation. Our results show that the Monte Carlo method could accurately predict the dose values to within 2%[20].

Additionally, an anthropomorphic phantom has been developed for further testing (see picture above). We believe that this phantom, with an actual breast and lung contour, will allow a more realistic benchmarking and comparison of competing treatment techniques for the breast. Furthermore, once MERT move into clinical treatment, this phantom will be absolutely essential for detailed quality assurance prior to each patient's treatment with MERT. This new phantom, shown here, has an outer material is tissue equivalent polystyrene and the material used to simulate lung is cork. It will support both film and TLD dosimetry.

5. Evaluate the efficacy of MERT treatments for breast cancer

A MERT system has been investigated, which consists of a set of software tools to perform accurate dose calculation, treatment optimization, and plan analysis. For this study, we have compared breast treatment plans (with and without nodal involvement) generated using MERT, IMRT and conventional tangential photon beams. The MERT plans were derived using our own treatment optimization software with up to 3 gantry angles and 5 nominal energies (6, 9, 12, 16, 20 MeV beams from a Varian Clinac 2100C accelerator). The tangential photon treatment plans were derived using the CMS FOCUS 3D treatment planning system with 6 MV wedged photon beams. A 6 MV anterior-posterior field was also used if there was nodal involvement. The IMRT plans were derived using the NOMOS CORVUS treatment optimization system with the same tangential beam angles of 6 MV x-rays. To remove any inconsistencies between the dose calculation algorithms used in the treatment planning system, all the plans were recalculated using the Monte Carlo method. Our Monte Carlo code system also took into account the effects of organ motion due to respiration and the effects of photon and electron leakage through the MLC and scattering off the MLC leaves.

We describe one case in detail. For this case we generated four plans: (1) tangential wedged photon beams, (2) tangential IMRT, (3) 5-field IMRT and (4) MERT with 4 electron fields. All the photon beams used in this study were 6 MV from a Varian Clinac 2300CD accelerator (Varian Medical Systems, Palo Alto, CA). For the conventional tangential photon treatment, a pair of 15-degree (dynamic) wedges were used for the two beams incident at 55- and 235-degree gantry angles (with the bottom edges of the two beams aligned). The tangential photon IMRT beams were parallel-

opposed at 50- and 240-degree gantry angles. The IMRT photon plan consisted of 5 fields incident at 40-, 90-, 140-, 190- and 240-degree gantry angles. The 4 electron fields for MERT were 6, 9, 12 and 16 MeV, respectively, from a Varian Clinac 2100C accelerator. All the electron fields were incident at a gantry angle of 140 degrees.

Figure 7 shows the patient anatomy and the isodose distributions planned using conventional wedged tangential photon beams, tangential 2-field IMRT, 5-field IMRT and 4-field modulated electron therapy. The corresponding dose volume histograms for the target and normal tissues are shown in Figure 8. From the target dose volume histograms of the four treatment plans, we see similar target dose coverage. The 5-field IMRT is only slightly better than the tangential photon beams, either modulated by wedges or MLC. The MERT target dose is about 10% inhomogeneous compared to 5-7% using photon beams. However, all these differences are considered acceptable clinically. It should be mentioned that the MERT plan was optimized using the CTV directly while the photon plans were optimized with a 1-cm margin. When the effect of respiratory motion is considered the target coverage is likely to be similar for the four plans.

Significant differences were observed in the doses in the critical structures (lung and heart) between the four plans. Figure 7 shows the lung doses and the respective target doses. All the photon plans resulted in similar maximum lung doses (about 50 Gy) while the volumes receiving high doses (30-50 Gy) were reduced by about 50% with intensity modulation (intensity-modulated tangents or 5-field IMRT). As is well known, multiple-field IMRT usually improves target coverage and reduces the high dose in the nearby critical structures at a cost of increased volumes of normal tissues that receive low doses. It is confirmed in Figure 7 that a large volume of the lung received 5-10 Gy dose in the 5-field IMRT plan although the gain in target coverage is almost negligible. The increase in the low-dose lung volume could increase the risk of radiation-induced secondary cancers, which would be unfavorable for younger patients. It seems that intensity-modulated tangential photon beams are favorable since they can reduce the lung volumes receiving medium (10-30 Gy) and high (30-50 Gy) doses by almost 50% compared to the conventional wedged tangential plan for similar target coverage. In comparison, the MERT plan resulted the lowest lung dose (less than 25 Gy). The volumes receiving low doses were much less than those in the 4-field IMRT plan and were only slightly more than those in the two tangential plans.

Figure 8 shows the heart dose volume histograms for the four plans with their respective target DVHs. The MERT dose is clearly the lowest with the maximum heart dose around 20 Gy. All the photon plans resulted in similar maximum heart doses but the intensity-modulated tangential beams

resulted consistently lower doses compared to the conventional tangents while the 4-field IMRT only brought improvement in the medium and high heart doses. Considering that a large volume of the heart received low and medium doses in the 4-field IMRT plan and the similar effect on the lung and the little gain in target coverage, it is evident that the multiple field IMRT technique, which has been successfully applied in prostate, head and neck and other deep-seated tumors, is not favorable for superficial targets such as breast cancers.

In general, MERT provides better or similar target dose coverage compared with conventional wedged tangential photon beams and intensity-modulated tangential beams. Our results confirmed the findings of previous investigators that IMRT could reduce the dose to the lung, heart and contralateral breast compared to conventional tangential wedged beams (up to 5 Gy in the maximum dose). However, MERT reduces the maximum dose to the lung by up to 20 Gy and to the heart by up to 35 Gy compared to conventional tangential wedged beams. When respiration motion was considered with a 1 cm chest wall movement significant dose heterogeneities were found in regions where the tangential photon beams abut the anterior-posterior supraclav photon beams. The effect of respiratory motion on MERT dose distributions was very small since the modulated electron beams were incident normally or at relatively small oblique angles.

Key Research Accomplishments

- *Develop computer model for organ motion and setup uncertainty*: A model of organ motion has been developed. This model uses clinical computed tomography scan of actual breast cancer patients. Thus, the models are realistic estimates of patient positioning and immobilization. We have developed a model of setup uncertainty based on published data. Since it has been shown that setup uncertainty is a random process in radiotherapy, our model has been implemented based on the Gaussian distribution.

- *Implement organ motion and setup uncertainty models into Monte Carlo code*: We have implemented the organ motion model into our Monte Carlo code called MCDOSE. This model is implemented in a general sense and can also be applied to conventional treatments as well as MERT treatments that are calculated with MCDOSE. We have implemented our model of setup uncertainty in our MCDOSE Monte Carlo code.

- *Validation of the code*: The Code has been validated in a cylindrical PMMA phantom and compared with ion chamber measurements. Additionally, another phantom has been developed for further testing and associated quality assurance as this new treatment modality makes its way into the clinic. This uniqueness of this second phantom is that it is anthropomorphic is the shape of the phantom approximating a breast and the shape and density of the lung volume within the phantom.

- *Study of the effects of organ motion and setup uncertainty on optimization*: Our results show that the effects of organ motion and setup uncertainty limit the degree of optimization of the dose distribution if they are not included in the beamlet simulation for optimization. Once included, the effect of these uncertainties can usually be minimized. This can be done by direct optimization of the beamlet weights or by modifying the beam delivery sequence.

- *Evaluate the efficacy of MERT treatments for Breast Cancer*: There are two main benefits of using MERT over conventional photon beams; (1) the conformity of the dose to the target is greater, (2) dose to normal tissue beyond the target is less due to greater dose fall off using electron beams. Effects of organ motion and setup uncertainty can be characterized by a decrease in peak dose to

the target and an associated increase in the spread of the low dose region. However, we believe that these effects are acceptable trade-offs for greater target conformity and normal tissue sparing.

Reportable Outcomes

Peer-reviewed papers resulting from or supported in part by this grant:

- Song Y, Boyer AL, Pawlicki T, Xing L, Jiang SB, Yan Y, Ma C-M, Lee MC (2003) Modulated electron radiation therapy (MERT): A novel treatment modality for parotid cancers In Press, Technology in Cancer Research and Treatment.
- Ma C-M, Ding M, Li JS, Lee MC, Pawlicki T and Deng J (2003) A comparative dosimetric study on tangential photon beams, intensity-modulated radiation therapy (IMRT) and modulated electron radiotherapy (MERT) for breast cancer treatment Phys Med Biol 48:909-24.
- Ma CM, Pawlicki T, Lee MC, Jiang SB, Li JS, Deng J, Mok E, Yi B, Luxton G and Boyer AL, Energy- and intensity-modulated electron beams for radiotherapy, Phys. Med. Biol. (2000) 45: 2293-2311
- Li JS, Pawlicki T, Deng J, Jiang SB, Mok E and Ma CM, Validation of a Monte Carlo dose calculation tool for radiotherapy treatment planning, Phys. Med. Biol. (2000) 45: 2969-2985

Meeting abstracts resulting from or supported in part by this grant:

- Lo A, Song Y, Boyer AL, Pawlicki T and Xing L Combining IMRT and MERT for breast-conserving radiation therapy Scientific paper at the 89th Scientific Assembly and Annual Meeting of the Radiological Society of North America, November 30 – December 5, 2003, Chicago, IL., 2003.
- Ding M, Deng J, Li JS, Lee MC, Jolly J, Pawlicki T and Ma C-M, Investigation of dose correlation for organ motion, Oral presentation at the 43rd Annual Meeting of the American Association of Physicists in Medicine in Salt Lake City, Utah from July 22-26, 2001.
- Jolly J, Ding M, Pawlicki T, Chu J and Ma C-M, Monte Carlo simulation of the effect of thoracic motion on breast treatment, Oral presentation at the 43rd Annual Meeting of the American Association of Physicists in Medicine in Salt Lake City, Utah from July 22-26, 2001.
- Pawlicki T, Guerrero TM, Jiang SB, Deng J, Li JS, Boyer AL and Ma CM, The role of set-up uncertainty in intensity modulated treatment planning, Oral presetation at the 42nd Annual Meeting of the *American Society for Theraputic Radiology and Oncology*, Boston, MA, October 22 – October 26, 2000.

- Pawlicki T, Jiang SB, Li JS, Deng J and Ma C-M, Including setup uncertainty in Monte Carlo Dose Calculation for IMRT, Oral presentation at the 2000 World Congress on Medical Physics and Biomedical Engineering (in conjunction with the 42nd Annual Meeting of the *American Association of Physicists in Medicine*), Chicago, IL, July 23-28, 2000.

Funding applied for based on work resulting from or supported in part by this grant:

None

Conclusions

We have developed models of organ motion and setup uncertainty for implementation into our MCDOSE Monte Carlo code and these models have been successfully implemented into that code. Results indicate that if organ motion and setup uncertainty are not included in the pre-optimization beamlet simulations, then the beamlet weights and subsequent dose distributions are not truly optimized. Because of its superior capabilities to achieve dose conformity both laterally and in the depth direction, MERT can be developed into a useful modality for superficial targets, especially for the treatment of breast cancer. The advantages of MERT over the currently used treatment techniques include uniform target coverage and significantly reduced normal tissue toxicity. Our results showed that MERT provided significant (20 Gy) reduction in peak lung and heart dose compared to either conventional tangents or IMRT tangents. The breathing margin could be reduced because electron beams do not required direct tangential fields. There was an increase in the low dose region (< 5 Gy) in the use of electrons. The best target homogeneity was achieved with IMRT photons. MERT offered significant improvement over tangents for the plans shown, with dose heterogeneities dispersed throughout the target region. Ultimately, however, the ideal breast treatment may be a combination of MERT and IMRT and this is being investigated[21]. Because of the success of this research, further investigations are being carried out to use MERT for other treatment sites such as head and neck[22].

References

1. Buchholtz TA, Gurgoze E, Bice WS and Prestidge BR (1997) Dosimetric analysis of intact breast irradiation in off-axis planes. *Int J Radiat Oncol Biol Phys* 39:261-7.
2. Gyenes G, Gagliardi G, Lax I, Fornader T and Rutqvist LE (1997) Evaluation of irradiated heart volumes in stage I breast cancer patients treated with postoperative adjuvant radiotherapy. *J Clinic Oncol* 15:1348-53.
3. Cazzaniga LF, Bossi A, Cosentino D, Frigerio M, Martinelli A, Monti A, Morresi A, Ostinelli A, Scandolaro L, Valli MC and Besana G (1998) Radiological findings when very small lung volumes are irradiated in breast and chest wall treatment. *Radiat Oncol Inves* 6:58-62.
4. Fraass BA, Roberson PL and Lichter AS (1985) Dose to the contralateral breast due to primary breast irradiation. *Int J Radiat Oncol Biol Phys.* 11:485-97.
5. Muller-Runkel R and Kalokhe UP (1990) Scatter dose from tangential breast irradiation to the uninvolved breast. *Radiology* 175:873-6.
6. Moody AM, Mayles WP, Bliss JM, A'Hern RP, Owen JR, Regan J, Broad B and Yarnold JR (1994) The influence of breast size on late radiation effects and association with radiotherapy dose inhomogeneity. *Radiot Oncol* 33:106-12.
7. Ma CM (proposal start date, October 1998) Energy- and intensity-modulated electron beams for breast cancer treatment. *U. S. Army Medical Research and Material Command Breast Cancer Research Program, proposal number BC971292.*
8. Ma CM, Pawlicki T, Lee MC, Jiang SB, Li JS, Deng J, Mok E, Yi B, Luxton B and Boyer AL (2000) Energy- and intensity-modulated electron beams for radiotherapy. *Phys. Med. Biol.* 45: 2293-2311.
9. Nelson R, Hirayama H and Rogers DWO. (1985) *The EGS4 code system*, Stanford Linear Accelerator Center Report SLAC-265 (SLAC, Stanford, CA).
10. Ma C-M, Li JS, Pawlicki T, Jiang SB, Deng J, Lee MC, Koumrian T, Luxton M and Brain S, (2002) A Monte Carlo dose calculation tool for radiotherapy treatment planning, Med. Phys. 47:1671-89
11. Li JS, Pawlicki T, Deng J, Jiang SB, Mok E and Ma C-M, (2000) Validation of a Monte Carlo dose calculation tool for radiotherapy treatment planning, *Phys. Med. Biol.* 45: 2969-2985.
12. Ma C-M, Li T, Pawlicki T, Jiang SB, Deng J, Chen L, Wang R, Price RA, McNeeley S, Ding M, Fourkal E and Qin L (2002) MCSIM: A Monte Carlo dose verification tool for radiation therapy treatment planning and beam delivery. *Med Phys* 29:1316.

13. Ding M, Deng J, Li JS, Lee MC, Jolly J, Pawlicki T and Ma C-M (2001) Investigation of dose correlation for organ motion. Oral presentation at the 43rd Annual Meeting of the American Association of Physicists in Medicine in Salt Lake City, Utah from July 22-26.

14. Jolly J, Ding M, Pawlicki T, Chu J and Ma C-M, Monte Carlo simulation of the effect of thoracic motion on breast treatment. (2001) Oral presentation at the 43rd Annual Meeting of the American Association of Physicists in Medicine in Salt Lake City, Utah from July 22-26.

15. Samson MJ, van Sörnsen de Koste JR, de Boer HCJ, Tankink H, Verstraate M, Essers M, Visser AG and Senan S. (1999) An analysis of anatomic landmark mobility and setup deviations in radiotherapy for lung cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 43:827-32.

16. Schewe JE, Balter JM, Lam KL and Ten Haken RK (1996) Measurement of patient setup errors using port films and a computer-aided graphical alignment tool. *Med. Dosim.* 21:97-104.

17. Killoran JH, Kooy HM, Gladstone DJ, Welte FJ and Beard CJ. (1997) A numerical simulation of organ motion and daily setup uncertainties: implications for radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 37:213-21.

18. Leong J (1987) Implementation of random positioning error in computerized radiation treament planning systems as a result of fractionation. *Phys. Med. Biol.* 32:327-34.

19. Lujan AE, Ten Haken RK, Larsen EW and Balter JM. (1999) Quantization of setup uncertainties in 3-D dose calculations. *Med. Phys.* 26:2397-2402.

20. Ma C-M, Jiang SB, Pawlicki T, Chen Y, Li JS, Deng J and Boyer, AL (2003) A quality assurance phantom for IMRT dose verification *Phys Med Biol* 48:561-72.

21. Lo A, Song Y, Boyer AL, Pawlicki T and Xing L Combining IMRT and MERT for breast-conserving radiation therapy Scientific paper at the 89th Scientific Assembly and Annual Meeting of the Radiological Society of North America, November 30 – December 5, 2003, Chicago, IL., 2003.

22. Song Y, Boyer AL, Pawlicki T, Xing L, Jiang SB, Yan Y, Ma C-M, Lee MC (2003) Modulated electron radiation therapy (MERT): A novel treatment modality for parotid cancers In Press, Technology in Cancer Research and Treatment.

APPENDIX COVER SHEET

FIGURES 1-8

MANUSCRIPT

Figure 1: Schematic of three phases of the breathing cycle that are usd to determine the dose to the breast during respiration.

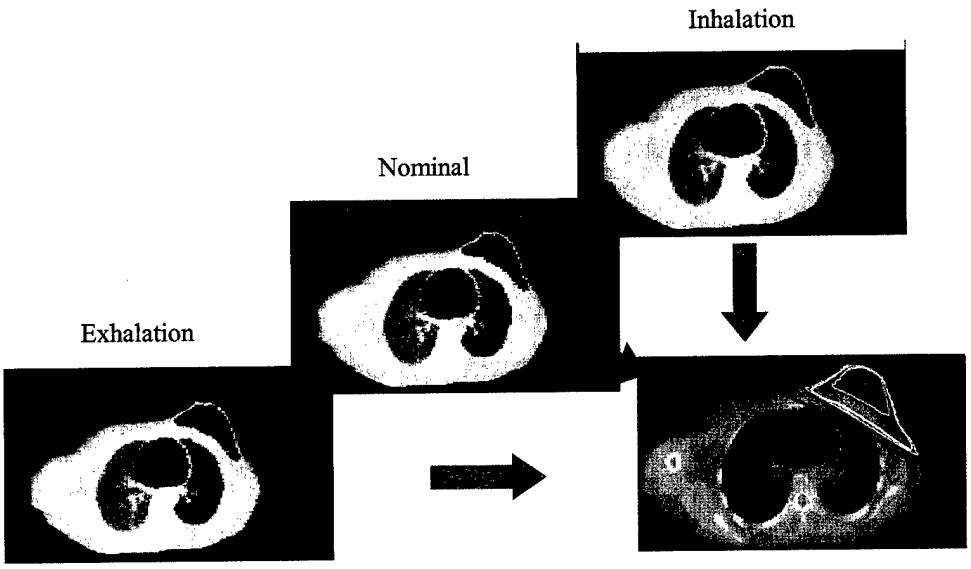


Figure 2: This is a schematic of our implementation of setup uncertainty in our Monte Carlo dose calculation code.

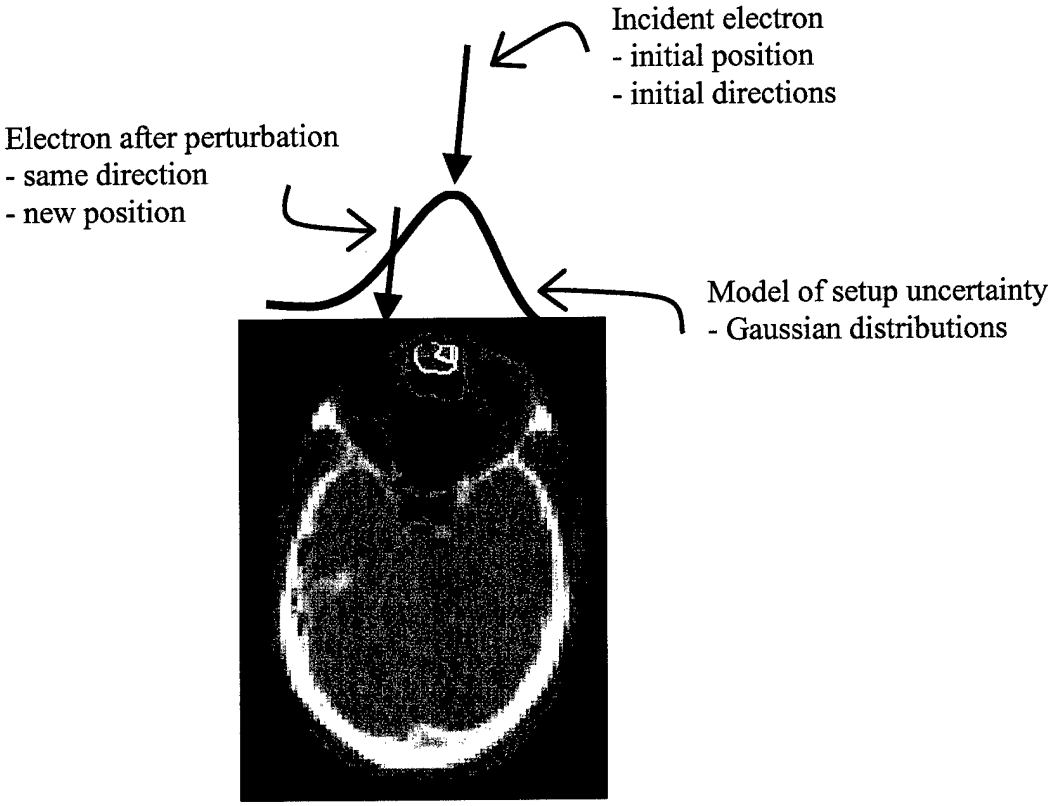
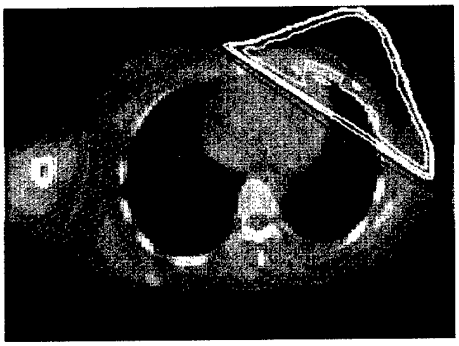
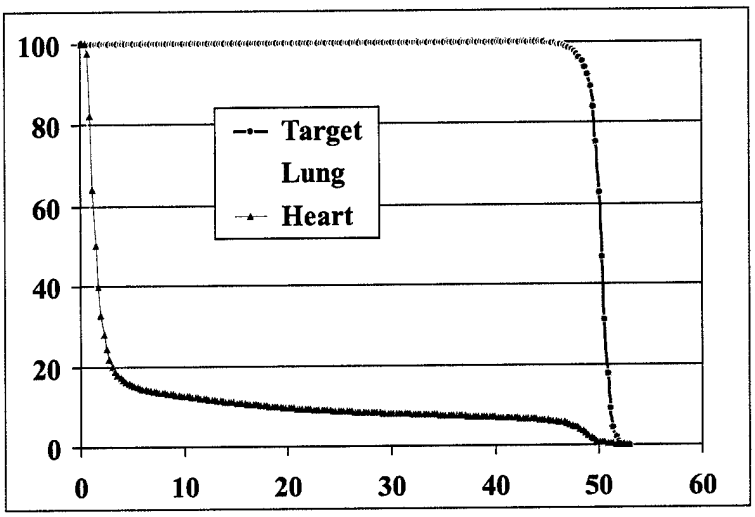


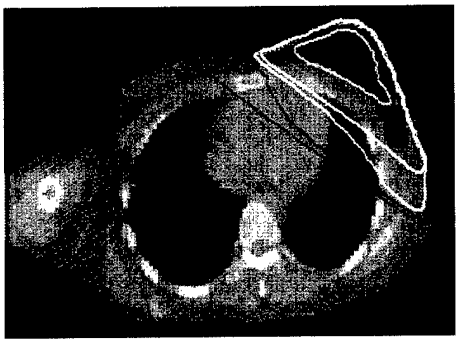
Figure 3:

(a) Static beams and static CT Contour.





(b) Static beams with organ motion. Note the degradation of the target coverage due to respiration.



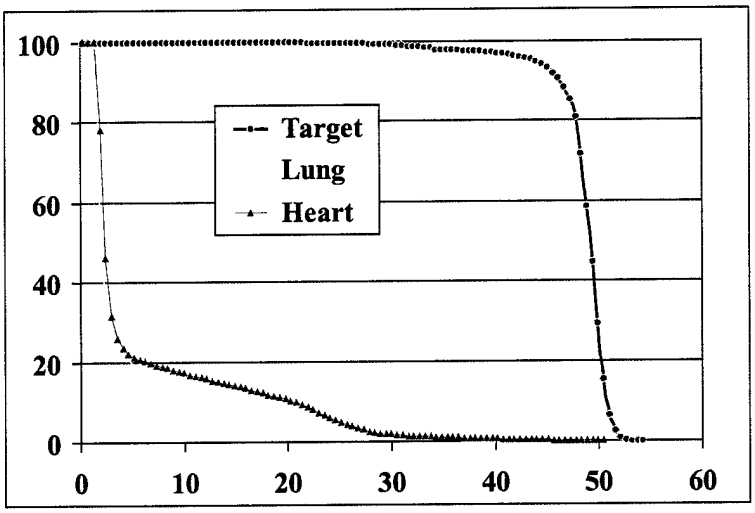
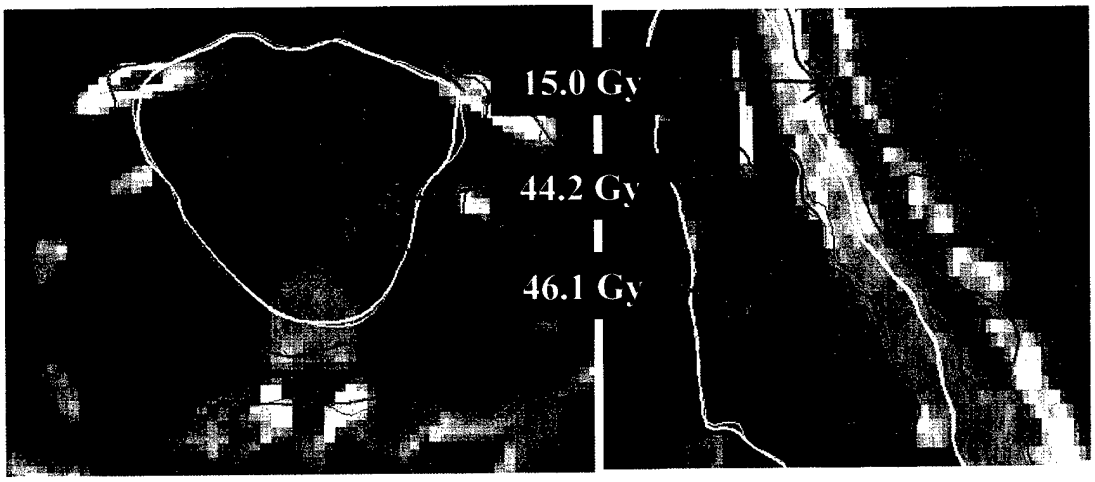


Figure 4:

(a) Axial and sagittal computed tomography slice showing the Monte Carlo calculated IMRT dose distributions with (thick line) and without (thin line) setup uncertainty included. The target is shown in green and the spinal cord in red.



(b) This is the dose-volume histogram of the dose distributions shown in Figure 6. Note the increase in target dose homogeneity. However, there is also a corresponding slight increase in dose to the spinal cord. The calculation with setup uncertainty is shown in by the curves with closed circles and without setup uncertainty by the solid line.

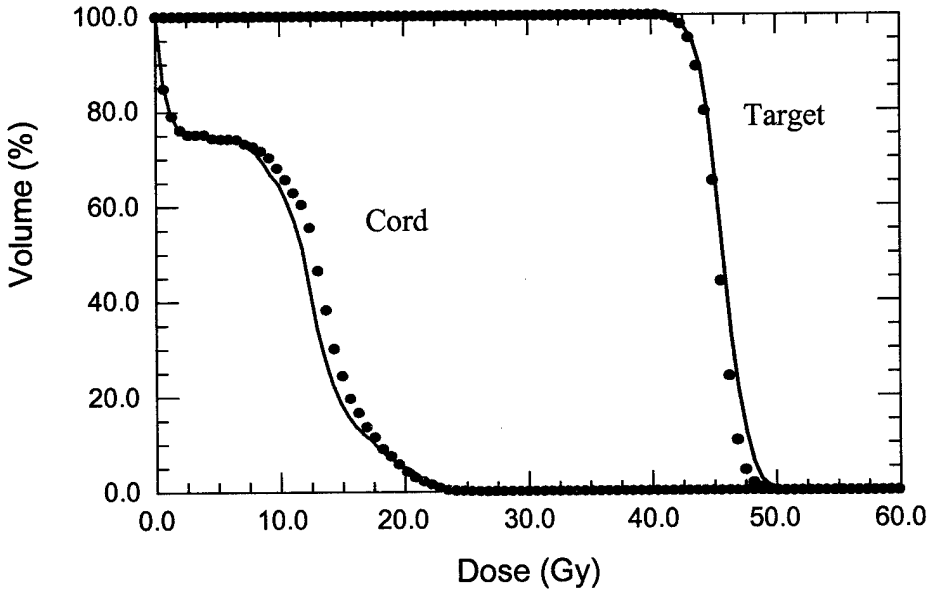


Figure 5: IMRT plan verification using a PMMA phantom with a bone insert. The ion chamber is also shown.

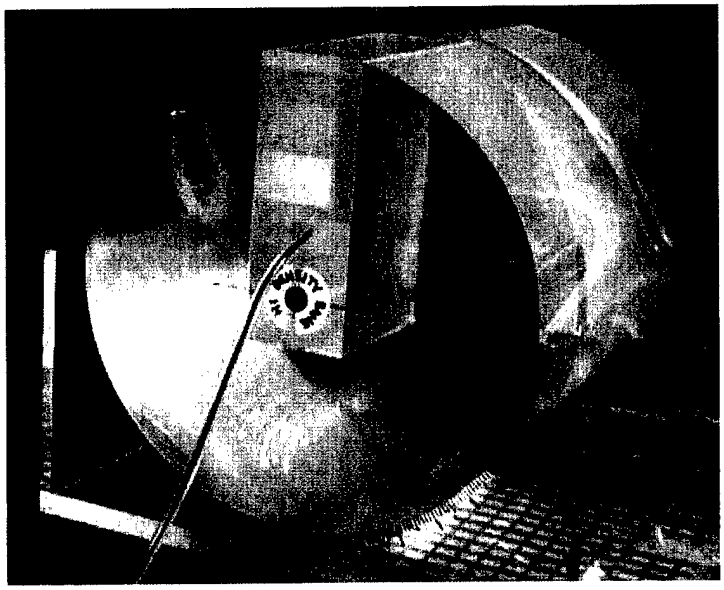


Figure 6: isodose distributions for the plan generated by CORVUS using 15 MV photon beams on a Varian Clinac 2300CD accelerator

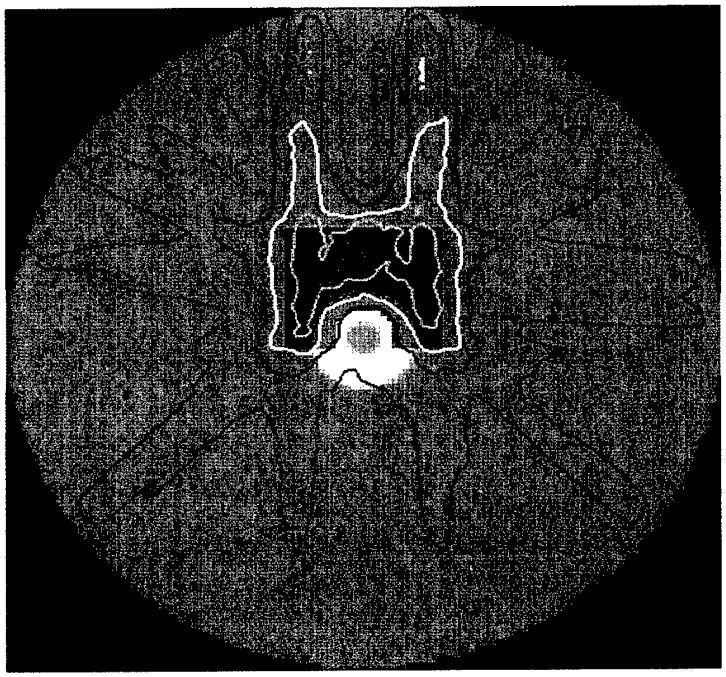
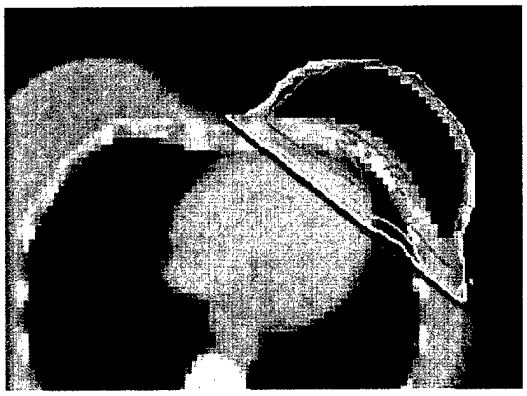
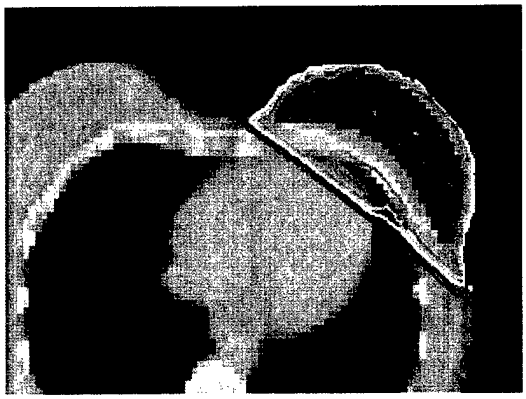


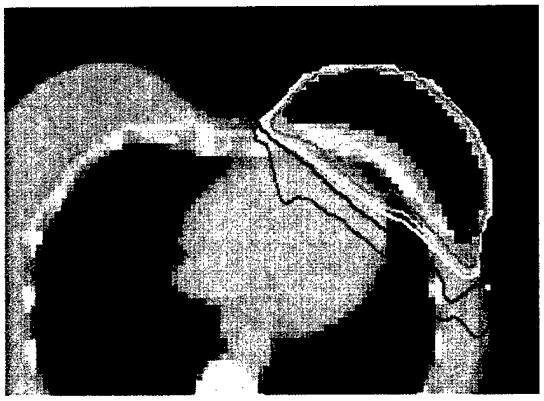
Figure 7: Isodose distributions for the patient planned using wedged tangential photon beams (a), intensity-modulated tangential beams (b), 5-field IMRT (c) and 4-field MERT (d). The 50, 45, 40, 30 and 20 Gy isodose lines are shown.



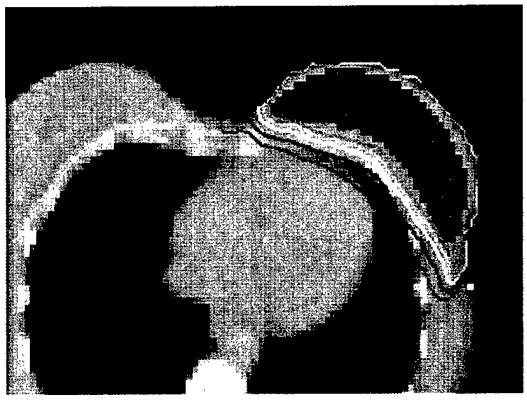
a



b

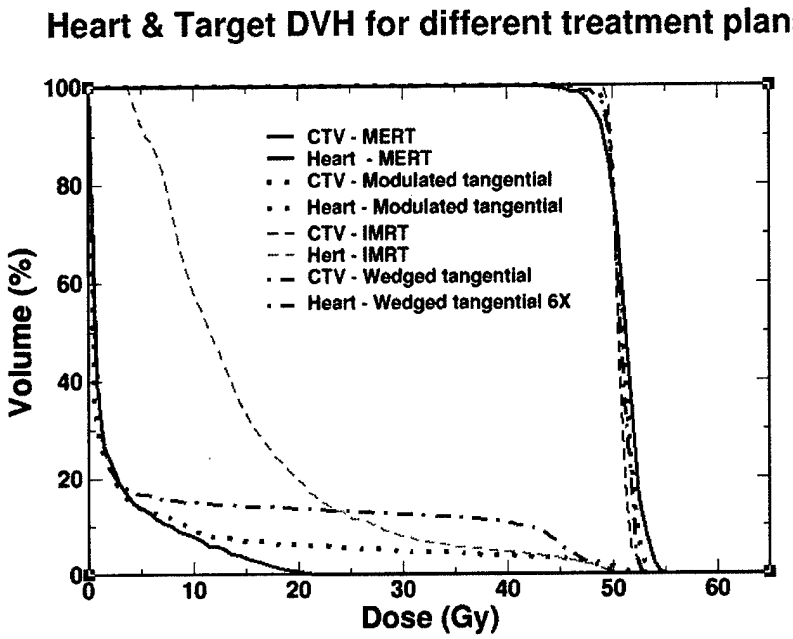


c

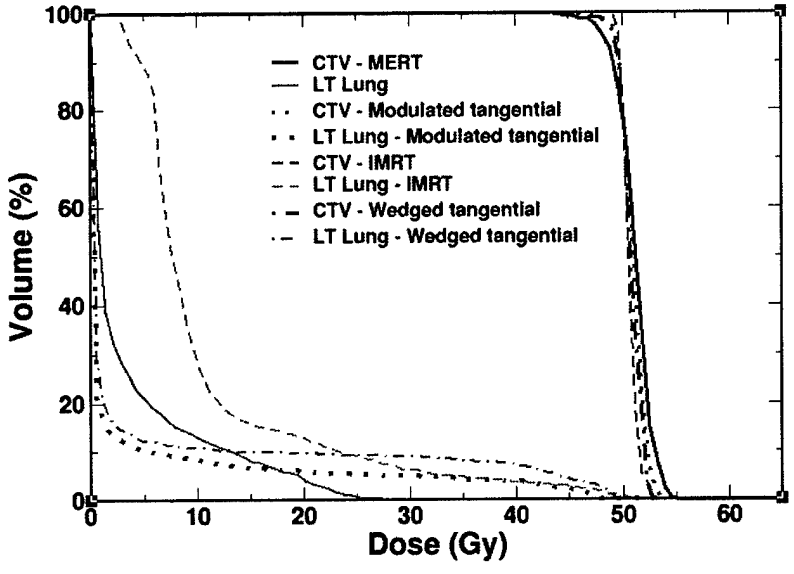


d

Figure 8: Dose volume histograms for the target and lung (a) and the target and heart (b) for the four treatment plans for the patient shown in Figure 7.



a



b

List of manuscripts submitted with this report

1. Ma C-M, Ding M, Li JS, Lee MC, Pawlicki T and Deng J (2003) A comparative dosimetric study on tangential photon beams, intensity-modulated radiation therapy (IMRT) and modulated electron radiotherapy (MERT) for breast cancer treatment Phys Med Biol 48:909-24.

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Phys. Med. Biol. 48 (2003) 909–924 PII: S0031-9155(03)58163-5

A comparative dosimetric study on tangential photon beams, intensity-modulated radiation therapy (IMRT) and modulated electron radiotherapy (MERT) for breast cancer treatment

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Abstract

Recently, energy- and intensity-modulated electron radiotherapy (MERT) has garnered a growing interest for the treatment of superficial targets. In this work, we carried out a comparative dosimetry study to evaluate MERT, photon beam intensity-modulated radiation therapy (IMRT) and conventional tangential photon beams for the treatment of breast cancer. A Monte Carlo based treatment planning system has been investigated, which consists of a set of software tools to perform accurate dose calculation, treatment optimization, leaf sequencing and plan analysis. We have compared breast treatment plans generated using this home-grown treatment optimization and dose calculation software for these treatment techniques. The MERT plans were planned with up to two gantry angles and four nominal energies (6, 9, 12 and 16 MeV). The tangential photon treatment plans were planned with 6 MV wedged photon beams. The IMRT plans were planned using both multiple-gantry 6 MV photon beams or two 6 MV tangential beams. Our results show that tangential IMRT can reduce the dose to the lung, heart and contralateral breast compared to conventional tangential wedged beams (up to 50% reduction in high dose volume or 5 Gy in the maximum dose). MERT can reduce the maximum dose to the lung by up to 20 Gy and to the heart by up to 35 Gy compared to conventional tangential wedged beams. Multiple beam angle IMRT can significantly reduce the maximum dose to the lung and heart (up to 20 Gy) but it induces low and medium doses to a large volume of normal tissues including lung, heart and contralateral breast. It is concluded that MERT has superior capabilities to

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achieve dose conformity both laterally and in the depth direction, which will be well suited for treating superficial targets such as breast cancer.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Recent advances in science and technology have brought significant improvement in radiation therapy. New treatment techniques have been developed to achieve dose distributions that can provide high degrees of target dose conformity and homogeneity. Intensity-modulated radiation therapy (IMRT) has been developed and implemented clinically as an advanced form of three-dimensional conformal radiation therapy (3DCRT) that utilizes computer-controlled multileaf collimators (MLC) for intensity-modulated beam delivery and inverse-planning techniques for treatment optimization (Brahme 1988, Convery and Rosenbloom 1992, Webb 1992, Mackie *et al* 1995, Yu *et al* 1995). IMRT uses multiple photon fields (ports) and variable fluence in these fields to achieve conformal dose to the target volume and to reduce the high dose to the nearby critical structures (often at the cost of spreading doses in larger volumes of normal tissues). Although IMRT has been used successfully for treating deep-seated tumours, such as prostate, head and neck (e.g., Ling *et al* (1996), Boyer *et al* (1997), Verellen *et al* (1997), Sultanem *et al* (2000), Price (2002)), it has been found less effective for superficial tumours such as breast tumours.

Conventional radiotherapy treatments of breast cancers use two tangential photon beams to avoid, as much as possible, irradiating the lung and the heart (for left breast treatment). Wedges are often used to improve target dose homogeneity. Smitt *et al* (1997) investigated IMRT for breast treatments and showed significant volumes of lung receiving low (<10 Gy) and medium (10–30 Gy) doses when multiple IMRT photon fields were used. These lung doses would not be clinically acceptable considering the potential late effects. Improvement of dose homogeneity produced using compensating filters has been shown to improve cosmesis (Taylor, 1995, Mayles *et al* 1991, Johnson *et al* 1996, Evans *et al* 1998, Carruthers *et al* 1999). Although 2D physical compensators derived from patient CT data can improve target dose homogeneity compared to conventional 1D wedges their widespread implementation remains impractical in many institutions. In addition, physical compensators may increase the dose to the contralateral breast (Fontenla *et al* 1994). Other investigators have explored techniques using forward-planned field-in-field techniques, shielding contralateral breast and applying inverse-planned intensity modulated beam delivery for breast treatments to improve target dose conformity and homogeneity and to reduce the dose to the lung and heart (Jannson 1997, Chang 1999, Hong 1999, Kestin *et al* 2000, Lo *et al* 2000, Chui *et al* 2002, Vicini *et al* 2002).

Recently, modulated electron radiation therapy (MERT, Ma *et al* 2000b) has garnered increasing interest for treating superficial tumour. Both intensity- and energy/intensity-modulated electron beams have been investigated to conform the dose to the target near the surface (Leavitt *et al* 1990, Lief *et al* 1996, Hyodynmaa *et al* 1996, Zackrisson *et al* 1996, Ebert and Hoban 1997, Karlsson *et al* 1998). In the optimization process of MERT, lateral dose conformity is achieved by intensity modulation while along the beam direction it is achieved by modulating electron incident energy, making use of the sharp dose fall-off feature. Traditionally, electron beams are shaped using a cutout (or blocks) and beam penetration or intensity may be modified using a bolus (Klein *et al* 1996, Low *et al* 1992). However, it is time consuming to make such beam modifiers and the treatment time would be significantly increased if such beam modifiers were used for MERT. Efforts have been made to develop

electron-specific MLCs (eMLC) or to modify treatment head design for MERT beam delivery (Leavitt *et al* 1997, Karlsson *et al* 1999, Ma *et al* 2000b, Lee *et al* 2000, McNeeley *et al* 2002, Boyd *et al* 2002, Faddegon *et al* 2002). Different treatment optimization techniques have been developed for MERT, including beamlet-based 2-step optimization and aperture-based treatment optimization, which took into account the effect of bremsstrahlung leakage and electron scattering from the eMLC (Lee *et al* 2001, Deng *et al* 2002).

In this work, we perform a comparative dosimetric study to evaluate MERT, photon IMRT, intensity-modulated tangential photon beams and conventional wedged tangential photon beams for the treatment of breast cancer. We will describe our home-grown treatment planning system used for this study, which consists of a set of software tools to perform accurate dose calculation, treatment optimization, leaf sequencing and plan analysis. We will analyse treatment plans using the four treatment techniques with a focus on target dose homogeneity and dose reduction in the lung and heart. We will discuss the potential of MERT and intensity-modulated tangential photon beams for breast cancer treatment as an alternative to the conventional wedged tangential photon beam treatments.

2. Materials and method

2.1. Treatment optimization for MERT and IMRT

The MERT and IMRT plans were optimized using a home-grown treatment optimization system based on the work by Jiang (1998). This system has been used in previous studies on Monte Carlo based treatment optimization for photon IMRT and for modulated electron therapy (Jiang *et al* 1999, 2000, Pawlicki *et al* 1999, Ma *et al* 2000b, Pawlicki and Ma 2001, Lee *et al* 2001). For completeness, we briefly describe the system and the optimization process here. After the treatment goals are defined, which include the target dose requirements and dose-volume constraints for the critical structures, the number of beams, beam angles and nominal energies are selected. Beamlet dose distributions for these fields (ports) are calculated using Monte Carlo simulations (see section 2.2), which result in a set of dose deposition coefficients (defined as the relative dose contribution from a beamlet to a voxel in the patient geometry). The weights of individual beamlets are optimized in order to achieve the treatment goals, which results in a set of optimal weights (an intensity map) for each treatment field (port).

Our optimization algorithm uses a gradient search method. The objective function has a quadratic form for the target with two additional dose-uniformity constraints to ensure a uniform target dose distribution and to distinguish the clinical importance of cold and hot spots. For the critical structures, maximum-dose constraint and several levels of dose-volume constraints are assigned to each structure. For each objective function and constraint, an importance weight relative to the target objective function is assigned. All the constraints are mathematically transformed to the penalty functions of quadratic forms. The augmented objective function is a combination of the original objective functions and all penalty functions. The results of the optimization process are the intensity maps (beamlet weight distributions) for the individual fields (different gantry angles for photon beams and also different energies for electron beams). The same optimizer and plan parameters have been used for planning both IMRT and MERT in this work.

2.2. The Monte Carlo dose calculation

The EGS4 (electron gamma shower version, Nelson *et al* 1985) user code, MCDOSE (Ma *et al* 2002), was used in this work for the dose calculations. MCDOSE was designed for dose

calculations in a three-dimensional rectilinear voxel geometry. Every voxel (volume element) could be assigned to a different material and mass density based on the patient CT data (Ma *et al* 1999, 2002). The cross-section data for the materials used were available in a pre-processed PEGS4 cross-section data file. The voxel dimensions and materials were defined in a MCDOSE input file together with the transport parameters such as the energy cutoffs (ECUT and PCUT), the maximum fractional energy loss per electron step (ESTEPE), and the parameters required by PRESTA (Bielajew and Rogers 1987). Several variance reduction techniques have been implemented in the MCDOSE code to improve the calculation efficiency. These include photon interaction forcing, particle splitting, Russian roulette, electron range rejection and region rejection, particle track displacement and rotation, and correlated sampling. Detailed descriptions of these techniques and the validation of their implementation in MCDOSE have been given elsewhere (Li *et al* 2000, Ma *et al* 2000a, 2002).

For patient dose calculations, the simulation phantom was built from the patient's CT data with up to $128 \times 128 \times 128$ voxels (uniform in any dimensions). The side of a voxel varied from 0.2 to 0.4 cm. The organ contours were also obtained for dose calculation and analysis. The phase-space data were reconstructed using a multiple source model (Ma *et al* 1997, Ma 1998, Jiang *et al* 2001, Deng 2000). To simulate the dose distribution of a finite size beamlet used by the inverse planning process, particles were transported to the MLC plane and only those within the beamlet area were allowed to go through. This ignored the photon leakage as well as the photon and electron scattering by the MLC in the optimization process. The final IMRT and MERT dose distributions were computed based on the intensity maps reconstructed from the leaf sequences or a direct simulation of the segmented field collimated by an electron MLC, which took into account the photon leaf leakage and electron scattering effect (Ma *et al* 2000a, Lee *et al* 2001). MCDOSE produced data files that contained geometry specifications such as the number of voxels in all the three directions and their boundaries as well as the dose values and the associated (1σ) statistical uncertainties in the individual voxels and organs (structures). The EGS4 transport parameters were ECUT = AE = 700 keV, PCUT = AP = 10 keV and ESTEPE = 0.04. Sufficient (10^8–10^9) particle histories were simulated to achieve a 1σ statistical uncertainty of 2% or smaller for the target doses. The CPU time required for these simulations were about 1–3 h on a Pentium III 800 MHz PC with the variance reduction option switched on.

2.3. Treatment planning details

We have planned for tangential photon beams, IMRT and MERT on three breast patients. To investigate the effect of radiation therapy on the heart, all the patients were selected for left breast treatments. For patient 1, we generated four plans: (1) tangential wedged photon beams, (2) tangential IMRT, (3) five-field IMRT and (4) MERT with four electron fields. All the photon beams used in this study were 6 MV from a Varian Clinac 2300CD accelerator (Varian Medical Systems, Palo Alto, CA). For the conventional tangential photon treatment, a pair of 15° (dynamic) wedges were used for the two beams incident at 55° and 235° gantry angles (with the bottom edges of the two beams aligned). The tangential photon IMRT beams were parallel-opposed at 50° and 240° gantry angles. The IMRT photon plan consisted of five fields incident at 40°, 90°, 140°, 190° and 240° gantry angles. The four electron fields for MERT were 6, 9, 12 and 16 MeV, respectively, from a Varian Clinac 2100C accelerator. All the electron fields were incident at a gantry angle of 140°.

For patient 2, we also generated four plans: (1) tangential wedged photon beams, (2) tangential IMRT, (3) four-field IMRT and (4) MERT with eight electron fields. The gantry angles used for this patient were the same as those for patient 1 except for plan three in which

the 240° gantry angle was absent and for plan four in which the eight electron fields were incident at gantry angles of 119° and 164° , respectively. A 45° wedge was used for the lateral beam in the conventional tangential plan. As for patient 1, all the four photon fields were 6 MV and the electron energies were 6, 9, 12 and 16 MeV for each gantry angle in the MERT treatment plan.

For patient 3, we only generated three plans: (1) tangential wedged photon beams, (2) tangential IMRT and (3) MERT with four electron fields. The conventional tangential beams were parallel-opposed at 45° and 235° (fields collimated with a half-beam block) and a 45° lateral wedge was used. The tangential IMRT beams were 6 MV incident at the same gantry angles as the conventional tangential plan. The same four electron energies (i.e., 6, 9, 12 and 16 MeV) were used in the MERT plan with a 135° incidence.

In all the photon treatment plans, the planning target volume (PTV) included up to 1 cm margin in the posterior direction to account for the effect of respiratory motion. This margin did not extend into the lung but went up to the edge of the chest wall. Therefore, the tangential photon beams were aligned with the bottom field edges covering the PTV. The MERT plans did not include such an extended margin since the electron beam angles were more or less in the chest wall movement direction (or with a small angle). A 1 cm or less chest wall motion corresponded to a similar change in the electron source surface distance (SSD), which would at most result in a relative beam output change by 2–4% (Ding *et al* 2002a).

3. Results and discussion

In this work, we have performed theoretical studies on the dosimetric characteristics of breast plans using different treatment techniques. Figure 1 shows the patient anatomy and the isodose distributions for patient 1 planned using conventional wedged tangential photon beams, tangential two-field IMRT, five-field IMRT and four-field modulated electron therapy. The corresponding dose volume histograms for the target, lung and heart are shown in figure 2. From the target DVHs of the four treatment plans, we see similar target dose coverage. The five-field IMRT is only slightly better than the tangential photon beams, either modulated by wedges or MLC. The MERT target dose is about 10% inhomogeneous compared to 5–7% using photon beams. However, all these differences are considered acceptable clinically. It should be mentioned that the MERT plan was optimized using the CTV directly while the photon plans were optimized with a 1 cm margin. When the effect of respiratory motion is considered the target coverage is likely to be similar for the four plans (Ding *et al* 2002b).

Significant differences were observed in the doses in the critical structures (lung and heart) between the four plans. Figure 2(a) shows the lung doses and the respective target doses. All the photon plans resulted in similar maximum lung doses (about 50 Gy) while the volumes receiving high doses (30–50 Gy) were reduced by about 50% with intensity modulation (intensity-modulated tangents or five-field IMRT). As is well known, multiple-filed IMRT usually improves target coverage and reduces the high dose in the nearby critical structures at a cost of increased volumes of normal tissues that receive low doses. It is confirmed in figure 2(a) that a large volume of the lung received 5–10 Gy dose in the five-field IMRT plan although the gain in target coverage is almost negligible. The increase in the low-dose lung volume could increase the risk of radiation-induced secondary cancers, which would be unfavourable for younger patients. It seems that intensity-modulated tangential photon beams are favourable since they can reduce the lung volumes receiving medium (10–30 Gy) and high (30–50 Gy) doses by almost 50% compared to the conventional wedged tangential plan for similar target coverage. In comparison, the MERT plan registered the lowest lung dose

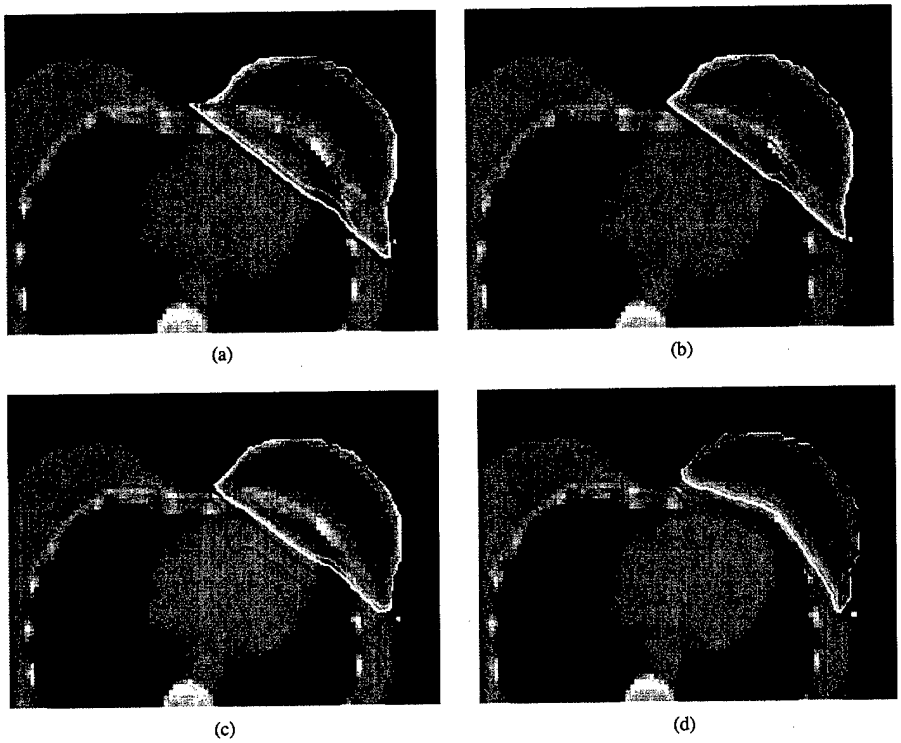
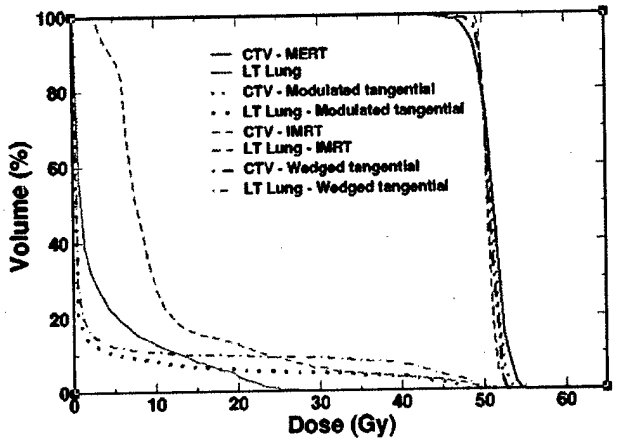


Figure 1. Isodose distributions for patient 1 planned using wedged tangential photon beams (a), intensity-modulated tangential beams (b), five field IMRT (c) and four field MERT (d). The 50, 45, 40, 30 and 20 Gy isodose lines are shown.

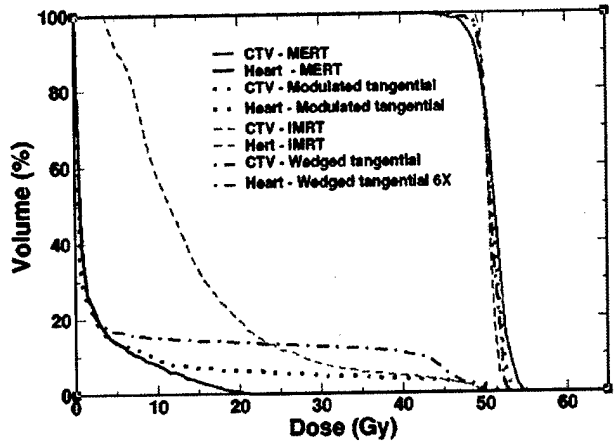
(less than 25 Gy). The volumes receiving low doses were much less than those in the five-field IMRT plan and were only slightly more than those in the two tangential plans.

Figure 2(b) shows the heart DVHs for the four plans for patient 1 with their respective target DVHs. The MERT dose is clearly the lowest with the maximum heart dose around 20 Gy. All the photon plans resulted in similar maximum heart doses but the intensity-modulated tangential beams resulted consistently lower doses compared to the conventional tangents while the five-field IMRT only brought improvement in the medium and high heart doses. Considering that a large volume of the heart received low and medium doses in the five-field IMRT plan and a similar effect on the lung and the little gain in target coverage, it is evident that the multiple field IMRT technique, which has been successfully applied in prostate, head and neck and other deep-seated tumours, is not favourable for superficial targets such as breast cancers.

Figure 3 shows the patient anatomy and isodose distributions for patient 2 planned using conventional wedged tangential photon beams, intensity-modulated tangential beams, four-field IMRT and eight-field MERT. The corresponding dose volume histograms for the target, lung and heart are shown in figure 4. Compared to patient 1, patient 2 had a thinner breast and a flatter (less curved) chest wall, and therefore represented a more favourable case for tangential beams since less lung and heart will be exposed to the photon beams. For easy



(a)



(b)

Figure 2. Dose volume histograms for the target and lung (a) and the target and heart (b) for the four treatment plans for patient 1.

comparison, we show DVHs for the target, lung and heart for the three-photon plans in figure 4(a). As usual, conventional tangents resulted in higher doses in the thinnest regions of the breast (superior and inferior borders near the apex). These region specific hotspots are most likely to manifest as clinical side effects, such as oedema. Greater flexibility in intensity modulation allowed IMRT tangents to correct for this, though hotspots in entrance tissue may still occur especially for large breasts. Without a medial beam the four-field IMRT plan resulted in a more heterogeneous target DVH for patient 2 compared to other photon plans and to the photon plans for patient 1. Similar conclusions can be made of the lung and heart DVHs for the three-photon plans for both patient 1 and patient 2.

It is interesting to compare the two intensity-modulated photon plans with the MERT plan (figure 4(b)). MERT has more dose heterogeneity (about 10%) in the target than IMRT

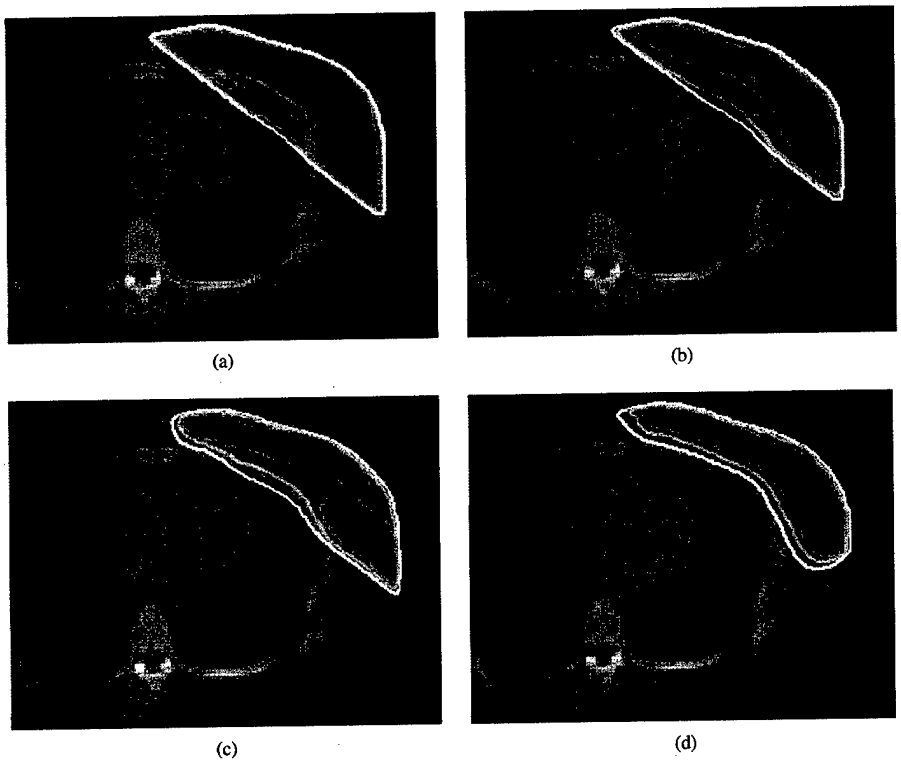
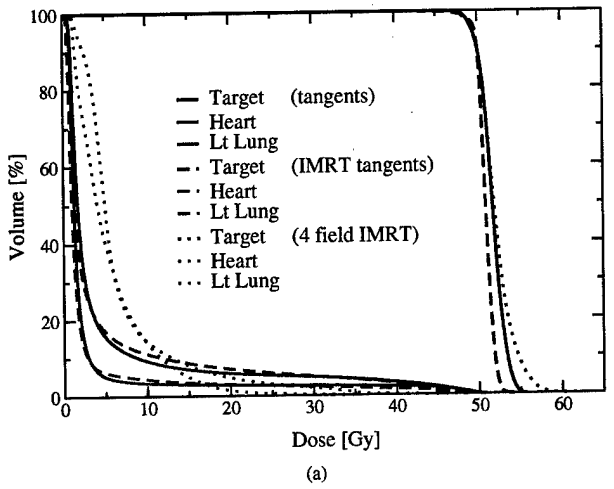
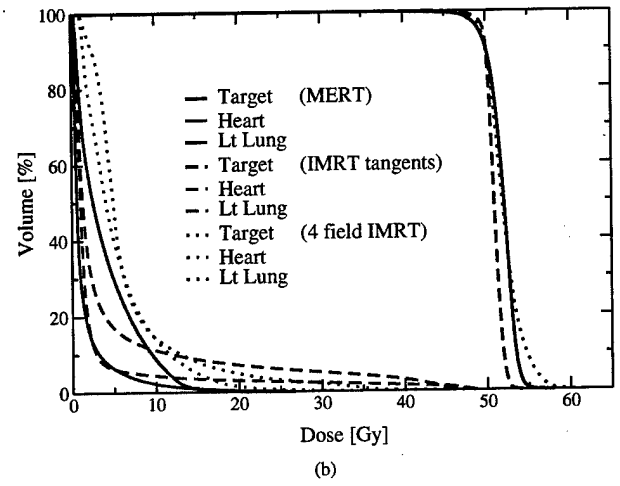


Figure 3. Isodose distributions for patient 2 planned using wedged tangential photon beams (a), intensity-modulated tangential beams (b), four field IMRT (c) and eight field MERT (d). The 55, 52.5, 50, 45, 40, 25, 15 and 5 Gy isodose lines are shown.

tangents (about 5%), but it is better than the four-field IMRT plan (about 15%). The lung and heart doses are much less than 20 Gy in the MERT plan. Unlike the photon plans, dose hotspots in the MERT plan were found to be more widely dispersed throughout the target region, not localized in specific geometric features. It seems clear that intensity-modulated tangents are better than the conventional tangents since they can bring definitive (more or less) improvement in the target, lung and heart dose–volume characteristics. This is understandable because both use medial and lateral beams to avoid the lung and heart and intensity-modulated tangents provide 2D dose compensation while conventional wedged tangents only provide limited 1D dose compensation. The multiple field IMRT technique was apparently inferior for both breast cases with significant lung and heart volumes receiving low and medium doses (see figure 5(a)). It was also evident based on the doses in healthy tissues (which represent everything inside the patient external contour minus the target volume) that multiple field IMRT was inferior to intensity-modulated tangents and MERT; over 5000 cc of healthy tissues received 5 Gy dose with four-field IMRT compared to less than 2000 cc with intensity-modulated tangents and MERT (figure 5(b)). Since radiation-induced fatal risk is proportional to the integral dose (total energy deposited in the body, which can be roughly estimated by the areas under the individual curves in figure 5(b)), it is likely that MERT as well as tangential IMRT are more beneficial than conventional tangents in terms of late effects. More detailed



(a)



(b)

Figure 4. Dose volume histograms for the target, lung and heart for the three photon beam plans (a) and the three intensity-modulated plans (b) for patient 2.

studies are needed to make a general conclusion since an accurate calculation of the fatal risk will require the precise knowledge of the total body dose, not just the dose in a portion of the body reconstructed from a limited set of CT scans, and also the contributions of accelerator head leakage and collimator scatter.

From the results above, it seems clear that multiple field IMRT does not provide significant improvement in target dose conformity and homogeneity while it results in large volumes of lung and heart (for left breast) exposed to low- and medium-doses that may lead to late effect. These results are consistent with the findings of previous studies (Smitt *et al* 1997). The question is whether intensity-modulated tangents bring enough improvement over conventional wedged tangents, and furthermore, whether modulated electron beams are worth

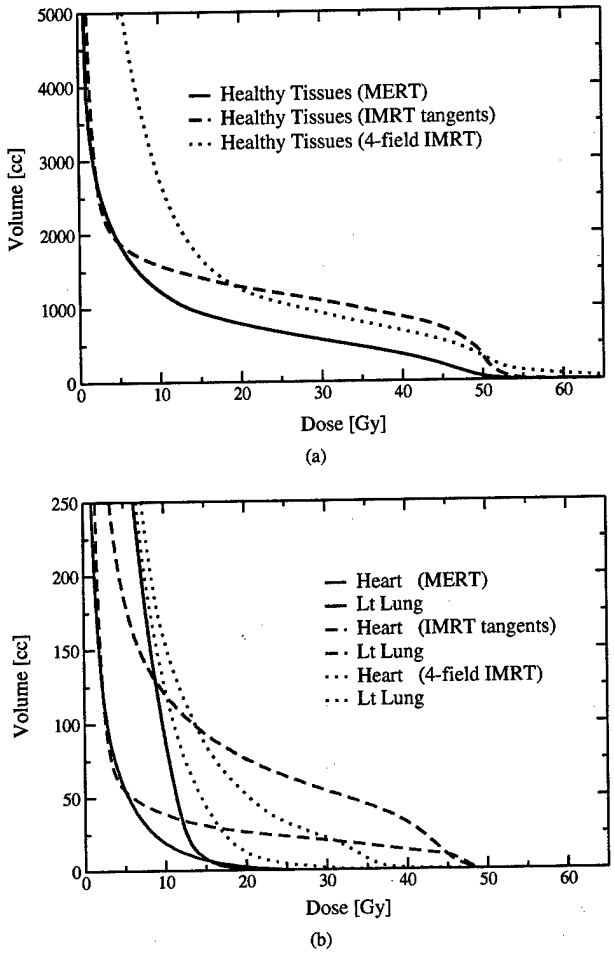
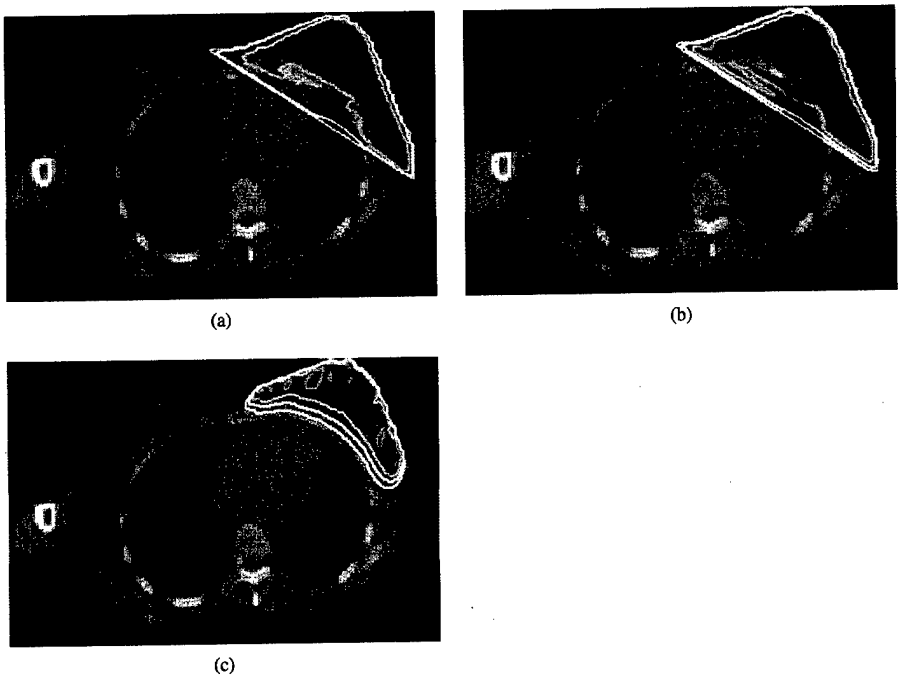


Figure 5. Healthy tissues, defined as all non-target volumes in the body receive the least dose in the MERT treatment. The residual electron range increases low lung dose, but the high dose regions are significantly reduced in normal tissues (a). Compared with tangential photon beams, MERT reduces both peak cardiac and lung doses by over 20 Gy. Almost no volume receives greater than 20 Gy in MERT (b).

further investigations of software and hardware development for breast cancer treatments. In figure 6, we show our third breast patient who had a relatively large target volume with significant volumes of lung and heart in the tangential beams due to the curved chest wall anatomy. Only MERT, tangential IMRT and conventional tangents were planned for this case with emphasis on the target dose homogeneity and no dose constraints on the lung and heart. The DVH curves for the target volume, lung and heart are shown in figure 7. As expected, the target dose was improved with intensity-modulated tangents since the target dose homogeneity was the only goal for the optimization. However, this was achieved at the cost of the lung and heart doses; both the lung and heart doses were increased slightly to improve the target



(a) (b)

(c)

Figure 6. Isodose distributions for patient 3 planned using wedged tangential photon beams (a), intensity-modulated tangential beams (b) and four field MERT (c). The 55, 50, 40, 30, 20 and 10 Gy isodose lines are shown.

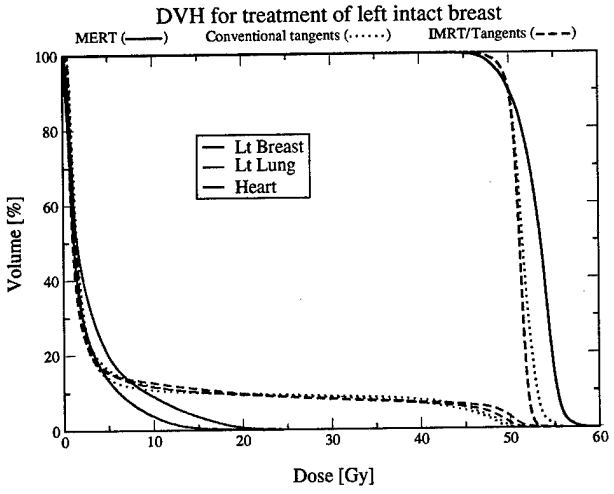
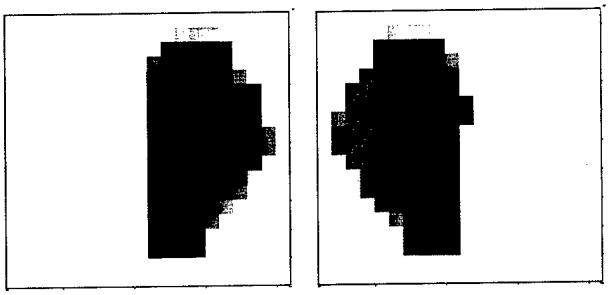


Figure 7. Dose volume histograms for the target, lung and heart for patient 3.

dose through the thicker portion of the breast. This was demonstrated by the intensity maps of the two tangential beams (figure 8). On the other hand, the MERT plan had about 10%



(a) medial (b) lateral

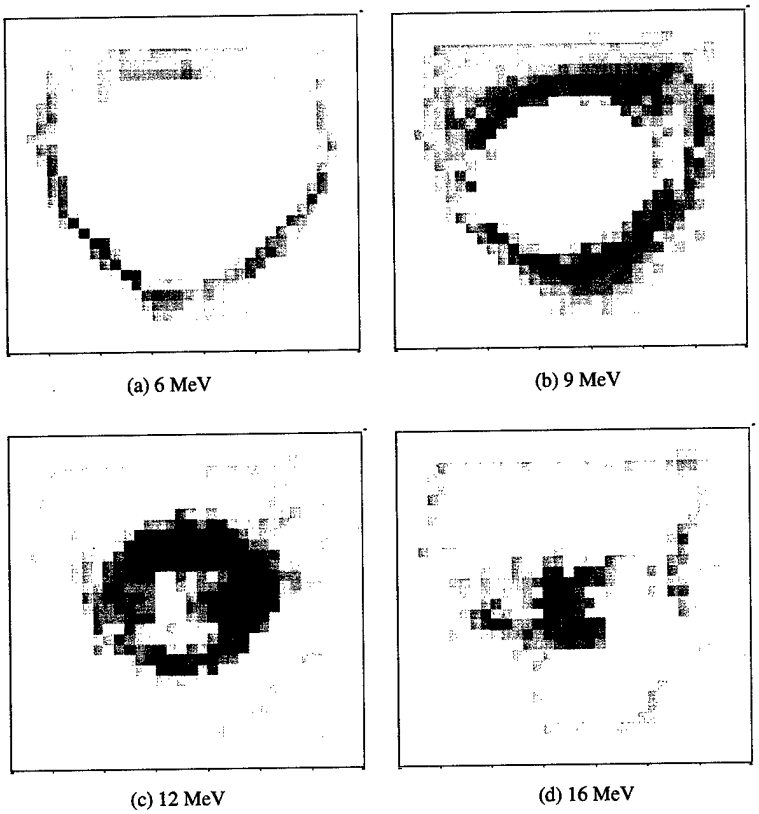
Figure 8. Intensity maps for the two intensity-modulated tangential photon fields for patient 3: (a) medial field and (b) lateral field.

Table 1. Relative dose values in 12 surface voxels of the CT phantom for patient 1 calculated using Monte Carlo simulations for different treatment techniques. The dose values are normalized to the prescribed target dose of 50 Gy, which covers 90% of the target volume.

6 MV	Medial (%)				Apex (%)				Lateral (%)			
Conventional tangents	55	62	68	86	88	96	98	84	78	76	66	63
IMRT tangents	56	66	70	83	87	93	96	84	68	64	62	69
Multi-field IMRT	56	64	74	77	80	90	88	82	74	67	64	66
MERT	89	92	99	96	94	99	101	93	91	95	87	70

dose heterogeneity in the target volume while the lung and heart DVHs were much improved compared to the photon beams. The maximum lung dose was under 20 Gy and the maximum heart dose was under 15 Gy compared to about 50 Gy for both photon plans. This was achieved by exposing low energy beams to the peripheral regions and higher energy beams in the central, thick portion of the target volume, as can be seen from the intensity maps for the four MERT beam energies (figure 9).

Finally, we want to discuss the issue of skin dose for energy- and intensity-modulated electron therapy. It is well known that photon beams have low entrance doses (40–50% for 6 and 10 MV beams at the skin surface) thus providing skin sparing for breast treatment. However, it is often needed to bring the skin dose up to ensure adequate skin dose coverage with the use of bolus or beam spoilers. The skin dose in these cases can be 50–80% of the prescription dose. Electron beams have higher entrance doses compared to photon beams; the per cent depth dose at the surface is about 70% for a 6 MeV beam and about 90% for a 20 MeV beam. Thus, the skin may be overdosed if electrons alone are used for breast treatment. In this work, the dose calculation was performed using 3D rectilinear voxel geometries built from patient CT data, which could not provide precise dose values on the skin surface. In table 1 we show the dose values in 12 voxels on the external contour for the photon and electron plans for patient 1. Since the voxels were about 3–4 mm in size, these dose values corresponded to depths 1.5–2 mm below the skin surface. The surface doses are lower in the medial and lateral aspects of the breast compared to those at the apex for tangential photon beams due to the difference in beam incident angle (obliqueness). The apex doses in the multiple field IMRT plan are slightly lower than those in the tangential plans since some beams are incident at less oblique angles. The MERT plan has the highest surface dose in comparison. In order to lower the surface dose it may be advantageous to combine MERT with intensity-modulated



(a) 6 MeV (b) 9 MeV

(c) 12 MeV (d) 16 MeV

Figure 9. Intensity maps for the four intensity-modulated electron fields for patient 3: (a) 6 MeV, (b) 9 MeV, (c) 12 MeV and (d) 16 MeV.

Table 2. Relative dose ranges in the contralateral breast of patient 1 calculated using Monte Carlo simulations for different treatment techniques. The dose values are normalized to the prescribed target dose of 50 Gy, which covers 90% of the target volume.

6 MV	Medial (%)	Apex (%)	Lateral (%)
Conventional tangents	2.5–5.0	0.6–3.0	<0.5
IMRT tangents	2.8–5.0	1.0–3.0	<0.5
Multi-field IMRT	10.0–18.0	6.0–15.0	5.0–8.0
MERT	1.0–5.0	0.5–1.0	<0.3

tangential beams. This will provide adequate skin dose and better lung and heart sparing compared to conventional tangential photon treatments. Table 2 shows the dose ranges in the contralateral breast for patient 1 using different treatment techniques. MERT resulted in similar doses in the medial aspects of the breast (mainly near the surface) but lower doses in the superficial and lateral aspects of the breast compared to tangential photon beams. Multiple field IMRT resulted in the highest doses in the contralateral breast among the four treatment techniques.

4. Conclusions

In this work, we have carried out a comparative dosimetric study on the dose distributions of MERT, IMRT and conventional photon treatment plans. All the plans were generated using the same treatment planning software. Treatment optimization was performed with the same dose requirement and constraints for MERT and IMRT. The final dose distributions were calculated using Monte Carlo simulations. Plan evaluation was carried out with an emphasis on target dose inhomogeneity as well as per cent volumes of normal structures receiving high, medium and low doses.

Our results showed that MERT provided significant (20 Gy) reduction in peak lung and heart dose compared to either conventional tangents or IMRT tangents. The breathing margin could be significantly reduced because electron beams do not require direct tangential fields. There was an increase in the low dose region (<5 Gy) in the use of electrons. The best target homogeneity was achieved with IMRT photons. MERT offered significant improvement over tangents for the plans shown, with dose heterogeneities dispersed throughout the target region.

The use of intensity-modulated electrons or photons may offer significant advantages over conventional treatments. However, continued research is necessary into aspects of beam planning and delivery for both photons and electrons. The ideal scenario may involve combined modulated electrons and photons, such as the use of MERT for tumour bed boosts or mediastinal node irradiation and photons for whole breast irradiation.

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References

Åsell M, Hyödynmaa S, Gustafsson A and Brahme A 1997 Optimization of 3D conformal electron beam therapy in inhomogeneous media by concomitant fluence and energy modulation *Phys. Med. Biol.* **42** 2083–100

Bielajew A and Rogers D W O 1987 PRESTA - the parameter reduced electron step algorithm for electron Monte Carlo transport *Nucl. Instrum. Methods* B **18** 165–81

Boyd R, Antolack J and Hogstrom K 2002 Dosimetric characterization of a prototype eMLC for fixed beam therapy *Med. Phys.* **29** 1285 (abstract)

Boyer A L, Geis P B, Grant W, Kendall R and Carol M 1997 Modulated-beam conformal therapy for head and neck tumors *Int. J. Radiat. Oncol. Biol. Phys.* **39** 227–36

Brahme A 1988 Optimal setting of multileaf collimators in stationary beam radiation therapy *Strahlenther. Onkol.* **164** 343–50

Carruthers L J, Redpath A T and Kunkler I H 1999 The use of compensators to optimize the three dimensional dose distribution in radiotherapy of the intact breast *Radiother. Oncol.* **50** 291–300

Chang S X, Deschesne K M, Cullip T J, Parker S A and Earnhart J 1999 A comparison of different intensity modulation treatment techniques for tangential breast irradiation *Int. J. Radiat. Oncol. Biol. Phys.* **45** 1305–14

Chui C S, Hong L, Hunt M and McCormick B 2002 A simplified intensity modulated radiation therapy technique for the breast *Med. Phys.* **29** 522–9

Convery D J and Rosenbloom M E 1992 The generation of intensity-modulated fields for conformal radiotherapy by dynamic collimation *Phys. Med. Biol.* **37** 1359–74

Deng J, Jiang S B, Li J S, Pawlicki T and Ma C M 2000 Photon beam characterization and modeling for Monte Carlo treatment planning *Phys. Med. Biol.* **45** 411–27

Deng J, Lee M C and Ma C-M 2002 A Monte Carlo investigation of fluence profiles collimated by an electron specific MLC during beam delivery for modulated electron radiation therapy *Med. Phys.* **29** 2472–83

Ding M, Li J S, Fourkal E, Chen L, Price R A, McNeeley S, Qin L and Ma C-M 2002a Impact of breathing motion on breast cancer treatment using electron and photon beams *Med. Phys.* **29** 1202 (abstract)

Ding M, Ma C-M, Li J S, McNeeley S, Chen L, Price R A, Fourkal E, Qin L, Anderson P and Freedman G 2002b Investigation of modulated electron radiation therapy for breast cancer *Int. J. Radiat. Oncol. Biol. Phys.* **54** 161 (abstract)

Ebert M A and Hoban P W 1997 Possibilities for tailing dose distributions through the manipulation of electron beam characteristics *Phys. Med. Biol.* **42** 2065–81

Evans P M *et al* 1998 Practical implementation of compensators in breast therapy *Radiother. Oncol.* **49** 255–65

Faddegon B A, Svatos M, Karlsson M, Olofsson L and Antolack J 2002 Treatment head design for mixed beam therapy *Med. Phys.* **29** 1285 (abstract)

Fontenla D P *et al* 1994 Effects of beam modifiers and immobilization devices on the dose in the build-up region *Int. J. Radiat. Oncol. Biol. Phys.* **30** 211–9

Hong L, Hunt M, Chui C, Spirou S, Forster K, Lee H, Yahalom J, Kutcher G J and McCormick B 1999 Intensity-modulated tangential beam irradiation of the intact breast *Int. J. Radiat. Oncol. Biol. Phys.* **44** 1155–64

Hyödynmaa S, Gastafsson A and Brahme A 1996 Optimization of conformal electron beam therapy using energy- and fluence-modulated beams *Med. Phys.* **23** 659–66

Jannson J *et al* 1997 Radiotherapy of breast cancer after breast-conserving surgery: an improved technique using mixed electron-photon beams with a multileaf collimator *Radiother. Oncol.* **46** 83–9

Jiang S B 1998 Development of a compensator based intensity modulated radiation therapy system *PhD Thesis* Medical College of Ohio, Toledo, OH

Jiang S B, Boyer A L and Ma C-M 1999 A hybrid system for IMRT inverse planning and dose verification *Int. J. Radiat. Oncol. Biol. Phys.* **41** 123 (abstract)

Jiang S B, Pawlicki T and Ma C-M 2000 An aperture-based inverse planning algorithm for modulated electron radiation therapy, in *Proc. Chicago 2000 World Congress on Medical Physics and Biomedical Engineering (Chicago, IL, July 23–28)* (long abstract)

Jiang S B, Deng J, Boyer A L and Ma C-M 2001 An extrafocal source model for photon beam dose calculation *Med. Phys.* **28** 55–66

Johnson J M, Potish R A and Khan F M 1996 Improved dose distribution with a universal acrylic breast compensator *Med. Dosim.* **21** 127–32

Karlsson M K, Karlsson M G and Zackrisson B 1998 Intensity modulation with electrons: calculations, measurements and clinical applications *Phys. Med. Biol.* **43** 1159–69

Karlsson M G, Karlsson M K and Ma C-M 1999 Treatment head design for multileaf collimated high-energy electrons *Med. Phys.* **26** 2125–32

Kestin L L, Sharpe M B, Frazier R C, Vicini F A, Yan D, Matter R C, Martinez A A and Wong J A 2000 Intensity modulation to improve dose uniformity with tangential breast radiotherapy: initial clinical experience *Int. J. Radiat. Oncol. Biol. Phys.* **48** 1559–68

Klein E E, Li Z and Low D A 1996 Feasibility study of multileaf collimated electrons with a scattering foil based accelerator *Radiother. Oncol.* **46** 189–96

Leavitt D D, Stewart J R and Earley L 1990 Improved dose homogeneity in electron arc therapy achieved by a multiple-energy technique *Int. J. Radiat. Oncol. Biol. Phys.* **19** 159–65

Lee M C, Jiang S B, Deng J, Li J S and Ma C-M 2001 Monte Carlo-based treatment planning for modulated electron beam radiation therapy *Phys. Med. Biol.* **46** 2177–99

Lee M C, Jiang S B and Ma C-M 2000 Monte Carlo and experimental investigations of multileaf collimated electron beams for modulated electron radiotherapy *Med. Phys.* **27** 2708–18

Li J S, Pawlicki T, Deng J, Jiang S B, Mok E and Ma C-M 2000 Validation of a Monte Carlo dose calculation tool for radiotherapy treatment planning *Phys. Med. Biol.* **45** 2969–85

Lief E P, Larsson A and Humm J L 1996 Electron dose profile shaping by modulation of a scanning elementary beam *Med. Phys.* **23** 33–44

Ling C C *et al* 1996 Conformal radiation treatment of prostate cancer using inversely-planned intensity-modulated photon beams produced with dynamic multileaf collimation *Int. J. Radiat. Oncol. Biol. Phys.* **35** 730–41

Lo Y C *et al* 2000 Intensity modulation for breast treatment using static multi-leaf collimators *Int. J. Radiat. Oncol. Biol. Phys.* **46** 187–94

Low D A, Starkshall G S, Bujnowsli W, Wang L L and Hogstrom K R 1992 Electron bolus design for radiotherapy treatment planning: bolus design algorithms *Med. Phys.* **19** 115–24

Ma C M 1998 Characterization of computer simulated radiotherapy beams for Monte Carlo treatment planning *Radiat. Phys. Chem.* **27** 329–44

Ma C M, Faddegon B A, Rogers D W O and Mackie T R 1997 Accurate characterization of Monte Carlo calculated electron beams for radiotherapy *Med. Phys.* **24** 401–16

Ma C-M, Li J S, Pawlicki T, Jiang S B, Deng J, Lee M C, Koumrian T, Luxton M and Brain S 2002 A Monte Carlo dose calculation tool for radiotherapy treatment planning *Phys. Med. Biol.* **47** 1671–89

Ma C-M, Mok E, Kapur A, Pawlicki T A, Findley D, Brain S, Forster K and Boyer A L 1999 Clinical implementation of a Monte Carlo treatment planning system for radiotherapy *Med. Phys.* **26** 2133–43

Ma C-M, Pawlicki T, Jiang S B, Mok E, Kapur A, Xing L, Ma L and Boyer A L 2000a Monte Carlo verification of IMRT dose distributions from a commercial treatment planning optimization system *Phys. Med. Biol.* **45** 2483–95

Ma C-M, Pawlicki T, Lee M C, Jiang S B, Li J S, Deng J, Yi B, Mok E and Boyer A L 2000b Energy- and intensity-modulated electron beam radiotherapy for breast cancer *Phys. Med. Biol.* **45** 2947–67

Mackie T R, Holmes T W, Reckwerdt P J and Yang J 1995 Tomotherapy: optimized planning and delivery of radiation therapy *Int. J. Imaging Syst. Technol.* **6** 43–55

Mayles W P M, Yarnold J R and Webb S 1991 Improved dose homogeneity in the breast using tissue compensators *Radiother. Oncol.* **22** 248–51

McNeeley S, Li J S, Price R A, Chen L, Ding M, Fourkal E and Ma C-M 2002 An electron specific MLC for modulated electron radiation therapy *Med. Phys.* **29** 1286 (abstract)

Nelson R, Hirayama H and Rogers D W O 1985 The EGS4 code system *Stanford Linear Accelerator Center Report* SLAC-265 (SLAC, Stanford, CA)

Pawlicki T A, Jiang S B, Deng J, Li J S and Ma C-M 1999 Monte Carlo calculated beamlets for photon beam inverse planning *Med. Phys.* **26** 1064–5

Pawlicki T and Ma C-M 2001 Monte Carlo dose modelling for MLC-based IMRT *Med. Dosim.* **26** 157–68

Price Jr R A, Hanks G E and McNeeley S W *et al* 2002 Advantages of using non-coplanar vs axial beam arrangements when treating prostate cancer with intensity modulated radiation therapy and the step-and-shoot delivery method *Int. J. Radiat. Oncol. Biol. Phys.* **53** 236–43

Smitt M C, Li S D, Shostak C A, Chang W and Boyer A L 1997 Breast-conserving radiation therapy: potential of inverse planning with intensity modulation *Radiology* **203** 871–6

Sultanem K, Shu H, Xia P, Akazawa C, Quivey J M, Verhey L J and Fu K K 2000 Three-dimensional intensity modulated radiotherapy in the treatment of nasopharyngeal carcinoma *Int. J. Radiat. Oncol. Biol. Phys.* **48** 711–22

Taylor M E, Perez C A, Halverson K J, Kuske R R, Philpott G W, Garcia D M, Mortimer J E, Myerson R J, Radford D and Rush C 1995 Factors influencing cosmetic results after conservation therapy for breast cancer *Int. J. Radiat. Oncol. Biol. Phys.* **31** 753–64

Verellen D, Linthout N, van den Berge D, Bel A and Syorme G 1997 Initial experience with intensity-modulated conformal radiation therapy for the treatment of the head and neck region *Int. J. Radiat. Oncol. Biol. Phys.* **39** 99–114

Vicini F A, Sharpe M, Kestin L, Martinez A, Mitchell C K, Wallace M F, Matter R and Wong J 2002 Optimizing breast cancer treatment efficacy with intensity-modulated radiotherapy *Int. J. Radiat. Oncol. Biol. Phys.* **54** 1336–44

Webb S 1992 Optimization by simulated annealing of three-dimensional conformal treatment planning for radiation fields defined by multi-leaf collimator: II. Inclusion of two-dimensional modulation of x-ray intensity. *Phys. Med. Biol.* **37** 1689–704

Yu C X, Symons J M, Du M N, Martinez A A and Wong J W 1995 A method for implementing dynamic photon beam intensity modulation using independent jaws and multileaf collimators. *Phys. Med. Biol.* **40** 769–87

Zackrisson B and Karlsson M 1996 Matching of electron beams for conformal therapy of target volumes at moderate depths *Radiother. Oncol.* **39** 261–70